CUTANEOUS MANIFESTATIONS OF INTERNAL MALIGNANCY

Dissertation Submitted in
fulfillment of the university regulations for

MD DEGREE IN
DERMATOLOGY, VENEREOLOGY AND LEPROSY
(BRANCH XII A)

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY
CHENNAI

MARCH 2008

CERTIFICATE

Certified that this dissertation entitled **"CUTANEOUS MANIFESTATIONS OF INTERNAL MALIGNANCY"** is a bonafide work done by **DR. A.AYYAM PERUMAL,** Post Graduate Student of the department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 600 003, during the academic year 2005 – 2008. This work has not previously formed the basis for the award of any degree.

Prof.Dr.B.PARVEEN, M.D.,D.D.,
Professor and Head of the Department,
Department of Dermatology and Leprology,
Madras Medical College,
Chennai-600 003.

Prof. Dr. T.P. KALANITI, M.D.,
Dean,
Madras Medical College,
Chennai-600 003.

SPECIAL ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr. T. P. Kalaniti, M.D**., Dean, Madras Medical College for allowing me to do this dissertation and utilize the institutional facilities.

ACKNOWLEDGEMENT

I am gratefully indebted to **Prof. Dr.B.PARVEEN, M.D.,D.D.,** Professor and Head, Department of Dermatology and Leprology for her invaluable guidance, motivation and help throughout the study. I would like to express my sincere and heartfelt gratitude to **Prof. Dr.V.S.Dorairaj, M.D., D.V.,** Director, Institute of Venereology.

I am very grateful to Dr.S.Jayakumar, M.D.,D.D., Additional Professor, Department of Dermatology for his invaluable guidance and help. I sincerely thank Dr.C.Janaki, M.D.,D.D., Reader of Dermatology (Mycology) for her priceless support.

I express my earnest gratitude to Dr.D.Prabhavathy, MD.DD**,** Professor and Head, Department of Occupational Dermatology and Contact Dermatitis for her constant motivation and guidance. I thank Dr.S.V.Somasundaram, MD.DD**,** Additional Professor, Department of Occupational Dermatology and Contact Dermatitis for his benevolent help and support.

I thank Additional Professor Dr.N.Kumar, M.D.D.V.,D.M.R.D., Institute of Venereology for his guidelines.

I wish to thank Dr.N.Gomathy, M.D.,D.D., Former Professor, Department of Dermatology and Dr.N.Usman, M.D.,D.V.,Ph.D, Former Director, Institute of Venereology for their constant support and motivation.

I offer my sincere thanks to Dr.G.K.Tharini, M.D., Assistant Professor, Department of Dermatology for her valuable guidance in conducting the study.

My sincere thanks go to Dr.V.Anandan, M.D., D.C.H., D.N.B (Paediatrics), Dr.R.Priyavathani,M.D., D.D.,D.N.B.,Dr.N.Hema, M.D., and Dr.S.Anupama Roshan, D.D.V.L., Assistant Professors, Department of Dermatolgoy for their kind support and encouragement.

I thank Dr.A.Hameedullah., M.D.,D.D., Dr.S.Kumaravelu, M.D., D.D., Dr.J.Manjula, M.D.,DNB and Dr.Afthab Jameela Wahab M.D.,D.D., Assistant Professors, Department of Occupational Dermatology and Contact Dermatitis for their support and help.

I am inclined to thank Dr.S.Mohan, M.D.,D.V., Former Registrar, Dr.V.Thirunavukarasu, M.D.,D.V., Dr.K.Venkateswaran, M.D.,D.V., Dr.S.Thilagavathy, M.D.,D.V., Dr.P.Mohan, M.D.,D.V., Dr.S.Arunkumar M.D.,D.V., Dr.S.Kalaivani, M.D.,D.V., and

Dr.P.Prabahar, M.D.(DVL) Assistant Professors, Department of Venereology, for their help and suggestions.

I express my sincere gratitude to Dr.K.Rathinavelu, MD.,DD.**,** **Former** Professor of Leprosy and Dr.R.Arunadevi, MD.,DD.**,** Lecturer/Registrar, Department of Dermatology for their support.

I also owe my thanks to Prof. V. Vedha Moorthy, M.D., D.M., Head of Department of Cancer Chemotherapy for all his help & for permitting me to use the clinical material in Cancer chemotherapy Department. I sincerely thank Dr. A. Lakshmi Narasimhan, M.D.D.M. Assistant Professor, Department of Cancer Chemotherapy, Madras Medical College.

I express my sincere gratitude to Prof. A.V.Shanthi, M.D., Director and Dr.P.Karkuzhli, M.D., Associate Professor, Institute of Pathology, Madras Medical College, for their invaluable guidance.

I duly acknowledge the paramedical staff and my colleagues for their help and favors. Last but not the least I am profoundly grateful to all patients for their co-operation and participation in this study.

CONTENTS

INTRODUCTION

Skin is a good mirror of internal diseases and gives more diagnostic clues than any other organs of the body. A wide range of cutaneous signs may be related to internal malignancy. Cancer may manifest in the skin as metastasis (e.g., leukemia cutis, cutaneous T-cell lymphoma, Paget's disease of the breast), nonspecific metabolic effects related to inanition (e.g., wasting, alopecia, xerosis), infections related to immunosuppression (e.g., herpes zoster), signs resulting from compromise or dysfunction of the affected organ (e.g., jaundice), or diverse dermatologic entities called paraneoplastic syndromes, which signal that a remote malignancy is present. Cutaneous manifestations may develop before a diagnosis of malignancy is determined; thus, these findings may aid the physician in the early identification of malignancy.

It is important to recognize the skin manifestations at the earliest for the following reasons.

1. Their easy accessibility

2. The skin lesions may be the presenting sign and recognized before the primary tumour[1].

3. The identification of these skin lesions in a known cancer patient under remission may be the first indication of recurrence.

4. It indirectly implies the prognosis of the internal malignancy[2].

A great challenge to the clinician is deciding when an aggressive evaluation for an occult malignancy is warranted and when conservative management is appropriate. Approximately 70% of cancers in patients with a presumed paraneoplastic condition can be detected with simple history taking, physical examination, and sex- and age-appropriate cancer screening. Unfortunately, most cutaneous paraneoplastic syndromes are associated with unresponsive cancers, and the prognosis is often poor.

REVIEW OF LITERATURE

Cutaneous paraneoplastic syndromes represent a heterogeneous group of dermopathies whose recognition may allow the early detection of occult malignancies. In some cases, the relationship between the skin findings and the underlying cancer is clearly established, and even the specific type of cancer may be revealed. However, other times, the significance of a given dermatologic syndrome is controversial.

There must be a proven association of the cutaneous eruption with a tumor. This is not difficult when the supposed manifestation is very rare and the tumor is also very uncommon. It becomes a major problem, however, when the manifestation is very common, such as the seborrhoeic keratoses in the sign of Leser-Trélat, and the presumed association is with a wide spectrum of commonly occurring neoplasms. In this situation the literature becomes replete with anecdotal reports, which may or may not be an indication of whether there is a true association with the malignant neoplasm[3].

There is an evolving consensus of what constitutes a true paraneoplastic syndrome. There are two essential criteria :

1. The dermatosis must develop only after the development of the malignant tumor, and

2. Both the dermatosis and the malignant tumor follow a parallel course, in that complete removal of the cancer results in clearing of the dermatosis and recurrence of the cancer causes relapse of the dermatosis.

These criteria have remained valid but perhaps overly stringent because cancers are often difficult to detect, and they may exert subtle physiologic influence without their presence being known. Study of these syndromes has contributed to the understanding of the biology of cancer skin.

Various attempts have been made to group these manifestations in a useful manner, but still our lack of knowledge does not allow us to classify these diseases by a pathophysiologic approach in all cases. Indeed, there is a very large group where the biochemical relationship to the neoplasia is not understood.

Cutaneous Manifestations of Internal Malignant Disease[3]

I. Lesions secondary to the deposition of substances in the skin

A. Icterus
B. Melanosis
C. Hemochromatosis
D. Xanthomas
E. Systemic amyloidosis

II. Vascular and blood abnormalities

A. Flushing
B. Palmar erythema
C. Telangiectasia
D. Purpura
E. Vasculitis
F. Cutaneous ischemia
G. Thrombophlebitis

III. Bullous disorders

A. Bullous pemphigoid
B. Pemphigus vulgaris
C. Paraneoplastic pemphigus
D. Dermatitis herpetiformis
E. Herpes gestationis
F. Erythema multiforme
G. Epidermyolysis bullosa acquisita
H. Linear IgA dermatosis

IV. Infections and infestations

A. Herpes zoster

B. Herpes simplex

C. Bacterial infections

D. Fungi and yeast infections

E. Scabies

V. Disorders of keratinization

A. Acanthosis nigricans

B. Acquired ichthyosis

C. Palmar hyperkeratosis

D. Tripe palm

E. Erythroderma

F. Paraneoplastic acrokeratosis of Bazex

VI. Collagen-vascular disease

A. Dermatomyositis

B. Lupus erythematosus

C. Progressive systemic sclerosis

VII. Skin tumors and internal malignant disease

A. Muir-Torre syndrome

B. Gardner's syndrome

C. Cowden disease

D. Mucosal neuroma syndrome

E. Neurofibromatosis

VIII. Hormone-related conditions

IX. Disorders associated with primary skin cancer

A. Nevoid basal cell carcinoma syndrome

B. Arsenical manifestations

X. Other disorders associated with internal malignant disease

A. Pruritus

B. Erythema gyratum repens

C. Subcutaneous fat necrosis

D. Sweet's syndrome and Neutrophilic dermatoses[4]

E. Hypertrichosis lanuginosa acquisita

F. Necrolytic migratory erythema

G. Clubbing

H. Peutz-Jeghers syndrome

I. Tuberous sclerosis

J. Multiple eruptive seborrhoeic keratoses

K. Porphyria cutanea tarda

XI. Direct tumor involvement in the skin

A. Direct Extension

B. Local Metastasis

C. Distant Metastasis

Color Changes Secondary to the Deposition of Substances in the skin :

ICTERUS

Icterus as a manifestation of internal malignancy is generally a late sign. It is usually secondary to obstruction of the bile duct or gross intrahepatic obstruction. Extrahepatic obstruction can be secondary to malignant disease of the gall bladder, pancreas, bile duct, or adjacent bowel.

Melanosis

Melanosis is a condition caused by the abnormal deposition of melanin pigments in tissue. It is externally manifested by a diffuse gray-brown pigmentation of the skin. A mild darkening of the skin may be seen with adrenal insufficiency, with ACTH-producing tumors such as primary tumors of the pituitary gland, or with other malignant tumors metastatic to the pituitary gland[6].

Diffuse melanosis and pigment streaks in the nail plate can also be secondary to malignant melanoma. Usually occurring late in the disease course, melanosis can, however, be the presenting sign.

Andreev and Petkov noted a melasma (chloasma) type of hyper pigmentation on the face of five patients with “brain tumors[7].” In

three patients the hyper pigmentation resolved after the surgical removal of the tumor.

Hemochromatosis

A diffuse gray-brown pigmentation of the skin can also be produced by Hemochromatosis. A third of untreated patients with hemochromatosis will develop hepatocellular carcinoma[8].

Xanthomas

The predominant type of xanthoma associated with internal malignant disease is the plane xanthoma. The most common association of diffuse plane xanthoma is with multiple myeloma. Xanthomas, as well as atypical eruptive histiocytosis with lipid deposition, have also been associated with myelocytic leukemia, myelomonocytic leukemia, leukemic lymphocytic reticuloendotheliosis, diffuse histiocytic lymphoma, and the cutaneous T cell lymphoma[9, 10]. Juvenile xanthogranuloma can be associated with juvenile chronic myeloid leukemia[11].

Purpura may be a feature of diffuse plane xanthomas associated with malignant disease. Pinch purpura has been noted in a normolipidemic patient with myeloma. Hemorrhagic bullae have been associated with xanthoma disseminatum and IgG K type multiple myeloma[12].

Systemic Amyloidosis

Systemic amyloidosis of both the primary type and that associated with multiple myeloma commonly has skin lesions. It is important to differentiate skin lesions of systemic amyloidosis from the far more commonly seen purely cutaneous variants of amyloidosis. All patients with skin lesions of systemic amyloidosis should be thoroughly investigated for multiple myeloma. Acute nonlymphocytic leukemia has also been reported in association with systemic amyloidosis treated with melphalan[13].

Intradermal bullae have been associated with myeloma-related amyloidosis. These bullae are the result of extensive dermal infiltration with amyloid, resulting in cleavage of the uppermost dermis from the lower dermis.

Vascular and Blood Abnormalities

FLUSHING

Acquired pronounced flushing, usually of the central face and upper trunk, may be a manifestation of carcinoid syndrome, caused by carcinoid tumors[14].

Vasoactive substances can also be released in patients with extensive localized or systemic mastocytosis and in patients with pheochromocytoma. Unilateral flushing and sweating (harlequin

syndrome) have been associated with a contralateral lung cancer invading the spine, in a patient with Pancoast's syndrome, and with Horner's syndrome[15].

Palmar Erythema

Palmar erythema can be associated with advanced liver failure. Such liver failure may be secondary to either a primary or a metastatic tumor in the liver.

Telangiectasia

Localized, grouped telangiectatic vessels on the anterior chest wall may be a marker for breast cancer. There is often a clinically palpable, indurated, warm, subcutaneous plaque immediately beneath the telangiectatic area. Generalized telangiectasia can be a presenting factor of malignant angioendotheliomatosis .Progressive telangiectases have been associated with carcinoid tumors and with adenocarcinoma of the hepatic bile duct[16].

Telangiectasia may also be a manifestation of a genodermatosis, which in turn can be associated with systemic malignant disease such as lymphoma.These genodermatoses include ataxia-telangiectasia, Bloom's disease, and xeroderma pigmentosum and its variant De Sanctis-Cacchione syndrome . In addition to the well-known association of lymphocytic leukemia and non-Hodgkin's

lymphoma in patients with ataxia-telangiectasia, there appears to be an increased incidence of solid tumors of the oral cavity, breast, stomach, pancreas, ovary, and bladder, as well as others[17]. Female heterozygotes of ataxia-telangiectasia have a significantly increased risk of breast cancer[18].

Purpura

Lymphoma is the most common cause of idiopathic thrombocytopenic purpura (ITP) associated with malignant disease. Hodgkin's disease is the most common associated lymphoma, and the diagnosis of ITP may precede other evidence of lymphoma.

Purpura related to cancer can occur from a wide variety of mechanisms: thrombocytopenia, consumption coagulopathy, hyper- or dysglobulinemia, vascular fragility, and vasculitis.

Disseminated intravascular coagulation (DIC) as a cause of purpura in malignant disease is most commonly associated with acute lymphocytic or myelomonocytic leukemia, in particular T cell acute lymphocytic leukemia[19]. Many patients may not have full-blown DIC, having only biochemical or mild clinical manifestations of the process. Thrombotic thrombocytopenic purpura, when associated with cancer, is usually a late sign.

Purpura can also be associated with the hyperglobulinemia seen in multiple myeloma or lymphoma. When purpura is secondary to the presence of cryoglobulins, lesions are often found in acral areas and may be associated with Raynaud's phenomenon. Benign hyperglobulinemic purpura can be associated with Sjögren's syndrome, which in turn can be associated with malignant disease.

Purpura, usually palpable, is a clinical sign of cutaneous vasculitis, which in turn can be associated with cancer. It is important not to forget that a bacterial septicemia can present as a palpable purpuric eruption in patients with cancer.

Vasculitis

Leukocytoclastic vasculitis, such as can be seen in Henoch-Schönlein purpura, can be very rarely associated with malignant neoplasms. It can be a presenting sign in squamous cell carcinoma, particularly of the bronchus[20], and in renal carcinoma[21]. Leukocytoclastic vasculitis can also be associated with leukemia and leukemic lymphoma[22].

A periarteritis nodosa–like syndrome has also been reported in association with hairy cell leukemia, acute lymphocytic leukemia, and multiple myeloma[23, 24].

Cutaneous Ischemia

Evidence of compromised peripheral circulation can be a marker for many malignant neoplasms. It is frequently manifested by evidence of digital ischemia, either as Raynaud's phenomenon or frank gangrene. Peripheral ischemia has been associated with many malignant neoplasms, including carcinoma of the pancreas, stomach, small bowel, ovary, and kidney, as well as lymphoma and leukemia[25]. The peripheral cutaneous ischemia secondary to the increased viscosity of the peripheral circulation can be seen in Polycythemia Rubra Vera[26], Leukemia, multiple myeloma and with lymphoma.

Thrombophlebitis

Isolated vein thrombophlebitis is uncommonly associated with internal malignant disease. Multiple-lesion “migratory” superficial thrombophlebitis is much more often seen in association with cancer, and when this syndrome is present the patient should be examined carefully for occult malignant disease. The association of peripheral thrombophlebitis with gastric carcinoma was noted by Trousseau in the nineteenth century.

Migratory superficial thrombophlebitis as a marker for cancer has been confirmed, and the association has been extended to include tumors of the pancreas, prostate, lung, liver, bowel, gallbladder, and

ovary, as well as to lymphoma and leukemia. The migratory nature of the thrombophlebitis probably relates to a generalized hypercoagulable state.

BULLOUS DISORDERS

Bullous Pemphigoid

There is probably no significantly increased risk of a malignant tumor in patients with bullous pemphigoid, other than that associated with the age of the patient[27], although a Japanese cohort of patients with bullous pemphigoid had a 5.8 percent prevalence of neoplasia, versus 0.61 percent of controls[28].

Pemphigus

Pemphigus vulgaris can be associated with Hodgkin's disease, in which case the two diseases can run a parallel course[29]. The relationship of solid tumors to pemphigus vulgaris is less well defined.

There is a well-defined association of pemphigus with thymoma, with or without clinical myasthenia gravis[30, 31, 32, 33].

Paraneoplastic pemphigus[34] is clinically, histopathologically, and immunopathologically a distinct form of pemphigus with features of erythema multiforme. It has been described in association with

lymphoma, chronic lymphocytic leukemia, thymoma, sarcoma, and Waldenström's macroglobulinemia; it has a very poor prognosis.

Dermatitis Herpetiformis

Dermatitis herpetiformis is occasionally associated with intestinal lymphoma. The relative risk of non-Hodgkin's lymphoma associated with dermatitis herpetiformis is 5.4 (2.2 to 11.1) in males, less in females[35]. Patients with dermatitis herpetiformis have gluten sensitivity, and the presumed etiology of the lymphoma is the resulting chronic antigenic stimulation.

Linear IgA Dermatosis

Linear IgA dermatosis has been reported in association with lymphoma, chronic lymphocytic leukemia, myeloma, carcinoma of the bladder and esophagus, and with hydatidiform mole[40,41].

Herpes Gestationis

Herpes gestationis has been described in association with a hydatidiform mole[36] and germ cell tumor[37].

Erythema Multiforme

Erythema multiforme does not appear to be a specific marker for any internal neoplasm. It appears to occur more frequently in patients

with acute leukemia, but whether this relates to the leukemia or to its treatment has not been well defined.

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita is a very rare disorder that has been described rarely in association with carcinoma of the bronchus and with amyloidosis and multiple myeloma[39].

INFECTIONS AND INFESTATIONS

Herpes Zoster

Only a small percentage of patients with localized herpes zoster have a concurrent malignant disease, and investigation for malignant disease in otherwise healthy patients is not indicated. Patients with leukemia or lymphoma do have an increased risk of herpes zoster, but the herpes zoster usually occurs late in the course of their disease. The incidence of herpes zoster in patients with lymphoma is approximately 10 percent, possibly even higher in patients with Hodgkin's disease[42].

Localized herpes zoster can also occur in association with solid tumors such as breast cancer. In the case of breast cancer, the dermatomal distribution of the herpes zoster may indicate involvement of the nerve root area with metastatic tumor. The site of the primary

tumor correlates with the site of herpes zoster in patients with breast cancer, cancer of the respiratory tract, and gynecologic cancer. Segmental herpes zoster can also occur after radiation therapy, presumably secondary to nerve damage with subsequent viral activation.

Disseminated herpes zoster is commonly associated with underlying malignant disease. Any patient with disseminated herpes zoster that is otherwise unexplained should be carefully examined for evidence of cancer.

The most commonly associated malignant diseases are lymphoma and leukemia[43]. The development of herpes zoster in a previously treated lymphoma patient can be evidence of the recurrence of a lymphoma. This sign is of particular value in patients who develop the herpes zoster more than 6 months after clinical remission[42].

Herpes Simplex

Typical localized herpes simplex is rarely a marker for cancer. Extensive, often chronic, local herpes simplex with massive ulceration and destruction of tissue, generalized cutaneous herpes simplex, and disseminated systemic herpes simplex are indeed associated with malignant disease, which is often far advanced. Lymphoma and

leukemia are most often the associated cancers, but any advanced malignant tumor can produce the compromised host immune response associated with these conditions[44].

Bacterial Infections

Bacterial infection of the skin as a marker for the presence of internal malignancy is very uncommon, and when it is associated with malignancy, it is usually associated with very advanced disease.]

Fungi and Yeast

Dermatophyte infections of the skin are not associated with internal malignant disease. Deep fungal infections, with their associated skin lesions, can be associated with malignant disease. Similarly, mucosal candidiasis usually indicates a severely compromised host immune response, which can be secondary to advanced malignant disease or to chemotherapy.

Scabies

Norwegian scabies, a severe generalized form of scabies, is associated with the leukemia-lymphoma group of neoplasms, but it can be seen in any severely immunocompromised host. The scabies is frequently manifested by a minimal inflammatory response and should

always be considered in patients who have advanced malignant disease associated with pruritus.

DISORDERS OF KERATINIZATION

Acanthosis Nigricans

Acanthosis nigricans can be classified into two major groups: benign and malignant. Malignant acanthosis nigricans is usually of sudden onset and is rapidly progressive, but it is otherwise clinically indistinguishable from benign acanthosis nigricans .Diffuse keratoderma involving the palms, soles, and flexor surfaces of the fingers and toes may be more common in malignant acanthosis nigricans than in the benign form. Such changes can be early.

Malignant acanthosis nigricans is usually secondary to an intraabdominal adenocarcinoma[45,46]. There is evidence that malignant acanthosis nigricans is linked to an enhanced secretion by the cancer of transforming growth factor alpha[47].

Acquired Ichthyosis.

Acquired ichthyosis (AI) is extremely rare and is virtually clinically indistinguishable from autosomal dominant ichthyosis vulgaris. Both conditions manifest with small white to brown polygonal scales that lift up at the free edge and are widely distributed on the

trunk and extensor surfaces of the extremities. The palms and soles are usually spared.

The sudden onset of ichthyosis in an adult may indicate an occult malignant tumor. AI is most strongly associated with Hodgkin lymphoma; as many as 70% of cases of paraneoplastic AI involve Hodgkin disease. Other AI-associated malignancies include Kaposi sarcoma, cutaneous T-cell lymphoma, non-Hodgkin lymphoma, leukemias, and solid tumors (including those arising in breasts, lungs, or bladder). The ichthyosis is a true hyperkeratosis and can be differentiated clinically and histologically from simple dry skin xerosis.

Palmar Hyperkeratosis

There are two groups of patients with palmar hyperkeratosis and associated malignant tumors: those patients with diffuse palmar hyperkeratosis and those with punctate palmar hyperkeratosis.

In 1958, diffuse hyperkeratosis, or tylosis, was reported by Howel-Evans et al[48] to be associated in two families with an almost certain development of esophageal carcinoma by age 65. The tylosis in these patients can be separated clinically from the benign form of tylosis, which occurs at an earlier age (early childhood), has sharply delimited edges, and is of uniform thickness. In addition to the Howel-Evans families, there would appear to be a greater than expected

incidence of esophageal carcinoma in other families with a pedigree of tylosis[49]. A large kindred has been described with palmoplantar keratoderma in association with breast or ovarian carcinoma, or both[50].

The second type of palmar hyperkeratosis that may be associated with neoplasia consists of discreet hyperkeratotic papules on the palms. These patients have been reported to have a greater than expected risk of cancer of the breast and uterus, among other tumors[51,52]. Palmar hyperkeratosis is also seen in paraneoplastic acrokeratosis of Bazex.

Tripe Palm

Tripe palm is a rugose thickening of the palms that is strongly associated with internal cancer[53]. The honeycombed and corrugated thickening of the palms may be associated with periungual tenderness[54]. Normal dermatoglyphic ridges are accentuated. The most common cancers associated with tripe palms are carcinomas of the stomach and lung, with fewer occurrences being noted with other solid tumors[55].

Erythroderma

Erythroderma, a diffuse erythema of the skin surface usually associated with induration and scaling, is not uncommonly associated with malignancy, most commonly hematologic, in particular leukemia

and lymphoma where there is direct infiltration of the skin by the malignant cells. The cells are most frequently lymphocytes of T cell type. Among solid tumors, erythroderma has been associated with carcinoma of the lung, liver, prostate, thyroid, colon, pancreas, and stomach.

Paraneoplastic Acrokeratosis of Bazex

Paraneoplastic acrokeratosis of Bazex is a symmetric dermatosis that most commonly affects the hands, feet, ears, and nose with an erythematous psoriasiform eruption. Acanthosis nigricans may be an associated finding. The nails are involved early and severely. There is subungual hyperkeratosis and flaky white surface of the nail. The nails may be shed. The distal digits show an erythematous scaling eruption, often fissured and often with suppuration[56,57]. Bazex syndrome is almost always associated with cancer, and is commonly seen in males[58]. It is usually associated with neoplasia of the upper respiratory system, which includes the pharynx, esophagus, tongue, and lungs, although rarely other solid tumors have been reported in association.

COLLAGEN-VASCULAR DISEASE

Dermatomyositis

Dermatomyositis can be a marker for internal neoplasia, and the

development of the dermatomyositis can predate the diagnosis of the cancer. The malignancies associated with DM are those common for the age, racial background, and sex of the patient, although incidences of ovarian, cervical, lung, and pancreatic and gastric carcinomas, in addition to non-Hodgkin lymphoma, may be unusually increased.

Clinical features of DM that may increase the likelihood of cancer include (1) a normal serum creatine kinase level, (2) disease that is refractory to treatment, (3) an absence of myositis antibodies, (4) overlap of autoimmune disease and lung disease, and (5) cutaneous necrosis. A review of the literature reveals that cancer risk is associated with increased age (>65 y), necrotic truncal lesions, the presence of cutaneous leukocytoclastic vasculitis, and capillary damage seen in muscle biopsy samples. Pediatric DM is only rarely associated with internal malignancy.

Lupus Erythematosus

Systemic lupus erythematosus (SLE) is only rarely associated with malignant neoplasia, most often with lymphoma or thymoma. Pemphigus erythematosus has been noted in association with malignant thymoma and myasthenia gravis, as has a pemphigus vulgaris–like eruption and positive LE cell test .

Scleroderma

Systemic scleroderma is not commonly associated with internal malignancy. In 727 cases of systemic scleroderma, only 2.6 percent had an internal malignant lesion[59]. The only tumor that has been found to be consistently associated with scleroderma is carcinoma of the lung[60]. Almost all patients with associated lung tumors have very advanced systemic scleroderma. The association is most likely one of a lung tumor developing secondary to the chronic pulmonary fibrosis.

SKIN TUMORS AND INTERNAL MALIGNANT DISEASE

Muir-Torre Syndrome

The essential features of the Muir-Torre syndrome are sebaceous tumors of the skin, with or without keratoacanthomas, in association with visceral neoplasms, which are often multiple[61,62]. Colon cancers are particularly common and may be associated with colonic polyposis[61,62,63,64,65]. Other neoplasms include other tumors of the gastrointestinal tract and tumors of the larynyx and endometrium. A solitary benign sebaceous gland tumor of the eyelid is a good marker for the Muir-Torre syndrome and that its presence warrants review for systemic cancer.

Gardner's Syndrome

The essential features of Gardner's syndrome are intestinal polyposis (usually colonic), with a high rate of malignant transformation; epidermoid cysts, particularly of the face, scalp, and trunk; osteomatosis of the maxilla, mandible, and cranial bones; and fibromas, desmoids, and other fibrous tumors of the skin and subcutaneous tissue[66]. There is an association of hepatoblastoma, a rare neoplasm of infants and children with Gardner's syndrome, and there may be some overlap of the features of Gardner's syndrome and nevoid basal cell carcinoma syndrome[67].

Cowden Disease

Cowden disease, or multiple hamartoma syndrome, inherited as an autosomal dominant trait, the distinctive cutaneous lesions are multiple tricholemmomas. These lesions are grouped around the mouth, nose, and ears and clinically resemble warts. Other cutaneous lesions can include lipomas, hemangiomas, neuromas, vitiligo, café au lait lesions, and acromelanosis[68]. Angioid streaks may be present in the retina.

Patients with Cowden disease have a greatly increased risk of breast and thyroid carcinoma. The breast changes seen in women range from fibrocystic disease to adenocarcinoma and can occur at a

young age. Prophylactic mastectomy may be indicated[69]. Thyroid adenoma is the most common thyroid tumor, but thyroid carcinoma can develop. Gastrointestinal tract polyposis is common[70]. There may also be an increased risk of gastrointestinal malignancy.

Mucosal Neuroma Syndrome

Mucosal neuroma syndrome is probably a variant of multiple endocrine neoplasia, type 2 (MEN 2 or 2A, Sipple's syndrome). Also designated MEN 3 or MEN 2B, the typical features include oral, nasal, upper gastrointestinal tract, and conjunctival neuromas, associated with medullary thyroid carcinoma (MTC) and pheochromocytoma. The appearance of the neuromas usually precedes the development of cancer, but the MTC can appear in early childhood. The pheochromocytomas are often bilateral. Unlike MEN 2, parathyroid hyperplasia is rare.

Neurofibromatosis

Von Recklinghausen's neurofibromatosis has many associated malignant tumors[71]. Malignant schwannoma is the most common, occurring in one series in 29 percent of patients[72]. These patients were usually over the age of 30. Other tumors include fibrosarcoma, rhabdomyosarcoma, nephroblastoma (Wilms' tumor), and acute and chronic myelogenous leukemia. There is an increased incidence of

ocular melanoma, with anecdotal reports of cutaneous melanoma. Benign neural tumors, peripheral and intracranial, are common.

HORMONE-RELATED CONDITIONS

Malignant tumors may release hormones into the circulation, and such hormones can produce skin manifestations. The manifestation of such hormone excess is not specific to the tumor and can occur secondarily from an excess of that hormone from any cause.

Hirsutism may be a manifestation of an increase in circulating androgens. Such androgen excess is most typically seen with testicular or ovarian tumors.

Gynecomastia in the male can be produced by an excess of estrogens. Such estrogens may be produced by a tumor of the testis. Lung tumors can also produce gynecomastia.

Cushing's syndrome is generally secondary to excessive ACTH production. Tumors from widely diverse sites can produce excessive ACTH. Many of these are derived from APUD tissue. The most common site is the lung, with the pancreas being the next most common.

Acne can be caused by the same tumors that produce hirsutism. Acne may also be a marker for internal malignancy in another way.

Female patients with severe acne show an apparent increase in the incidence of breast cancer[73].

OTHER DISORDERS ASSOCIATED WITH PRIMARY SKIN CANCERS

Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome, or Gorlin-Goltz syndrome, is a syndrome consisting of multiple basal cell carcinomas, jaw cysts, skin pitting, skeletal abnormalities, and a tendency to malignant disease[74]. The most common malignant tumor is medulloblastoma[75]. These tumors can occur in patients without any cutaneous basal cell carcinomas but with a family history of nevoid basal cell carcinoma syndrome. Other tumors include astrocytomas, meningiomas, and craniopharygiomas.

Arsenical Manifestations

Chronic arsenic toxicity can be manifested by arsenical melanosis, plantar and palmar keratoses, and Bowen's disease. There would also appear to be an increased risk of internal neoplasia. The increased cancer risk was originally estimated to be to nine times the expected incidence. Approximately one-third of patients with Bowen's disease developed an internal malignancy 6 to 10 years after their initial diagnosis[76]. Malignancies have included tumors of the urogenital

region, mouth, esophagus, and lung. Arsenical keratoses on the palms and soles, a more specific finding, did correlate with an apparent increase in internal malignancy[77].

OTHER DISORDERS ASSOCIATED WITH INTERNAL MALIGNANT DISEASE

Pruritus

Pruritus, often accompanied by excoriations, can be a nonspecific marker of internal malignant disease. Although often associated with xerosis, the pruritus of malignant disease can occur in apparently normal skin. It can be continuous or paroxysmal. It is usually generalized.

When occurring with malignant diseases, pruritus is most commonly associated with leukemia and lymphoma, including drug induced lymphoma[78]. Pruritus is one of the most common cutaneous manifestations of leukemia, probably exceeded only by purpura. It is usually less severe than that associated with lymphoma and is more often generalized. Pruritus associated with bathing is a marker for polycythemia rubra vera and is present in half of patients[79]. This itch can be severe and paroxysmal. Patients with polycythemia rubra vera can also have chronic continuous pruritus unrelated to bathing.

Severe pruritus can be a feature of Fanconi's anemia and myeloma. Pruritus associated with visceral neoplasia is most commonly associated with pancreatic and stomach tumors[80] but may also be associated with most other solid tumors. The appearance of severe pruritus after treatment of the primary tumor may herald a tumor recurrence. Renal and liver involvement with primary or metastatic cancer can also produce pruritus secondary to the accumulation in the skin of pruritogenic metabolites.

Erythema Gyratum Repens

Erythema gyratum repens is a cutaneous eruption consisting of concentric raised erythematous bands moving in waves over the body surface in a “wood-grain” pattern[81]. The erythematous bands may be flat or raised. Removal of the malignant tumor usually results in complete resolution of erythema gyratum repens within 6 weeks.

Almost all cases of erythema gyratum repens, which is extremely rare, are associated with internal malignancy. Although first described with carcinoma of the breast[81], erythema gyratum repens has also been found in association with tumors of the lung[82], bladder, prostate, cervix, stomach, and esophagus and with multiple myeloma.

Subcutaneous Fat Necrosis

Subcutaneous fat necrosis is a cutaneous marker for acinar cell carcinoma of the pancreas. Intraosseus fat necrosis can also occur[83], with the production of osteolytic lesions visible on x-ray examination. The polyarthralgia is presumably the result of fat necrosis of the periarticular tissue. There is frequently a concomitant associated fever and eosinophilia.

Sweet's Syndrome and Neutrophilic dermatoses

In Sweet syndrome,also termed acute febrile neutrophilic dermatosis[84], clinical lesions range from generalized crimson, agminate papules, to large red to purple-red plaques, to lesions that are truly bullous in nature, and to lesions that are indistinguishable from pyoderma gangrenosum. The skin lesions usually erupt suddenly. Malignancy associated Sweet's syndrome is most commonly seen with acute myelocytic leukemia but may also be observed in acute myelomonocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, multiple myeloma, and lymphoma.

Pyoderma gangrenosum, particularly in a superficial and bullous form, has been associated with myeloproliferative diseases, including

acute and chronic myeloid leukemia, acute lymphocytic leukemia, myeloid metaplasia, PRV, multiple myeloma, lymphoma and myelofibrosis[85,86]. Solid tumours reported included carcinoid, colon, bladder, prostate, breast, bronchus, ovary and adrenocortical carcinoma[86].

Hypertrichosis Lanuginosa Acquisita

Hypertrichosis lanuginosa acquisita (HLA) is an acquired excessive growth of lanugo (vellus) hairs. Fully expressed HLA is usually secondary to malignant tumors, but excessive lanugo hair growth can also be caused by drugs such as exogenous steroids, phenytoin, diazoxide, streptomycin, penicillamine, cyclosporine, and minoxidil or by conditions such as anorexia nervosa.

HLA secondary to malignancy is usually abrupt in its onset and is rapidly progressive. Associated tumors reported include tumors of the colon (including carcinoid tumors), rectum, bladder, lung, pancreas, gallbladder, uterus, breast and lymphoma[87,88,89].

Necrolytic Migratory Erythema

Necrolytic migratory erythema is a marker for an alpha-2-glucagon- producing islet cell tumor of the pancreas[90,91,92]. It is manifested by erythema, vesicles, pustules, bullae, and erosions, which typically involve the face, the intertriginous areas, in particular

the groin, and the perigenital region . It also involves the shins, ankles, and feet as well as the fingertips. Most patients with necrolytic migratory erythema have a pancreatic tumor of the glucagon-producing type. Resection of the tumor clears the eruption, sometimes within 48 h.

Clubbing

Clubbing is the soft tissue enlargement of the tips of the fingers and toes. More typically associated with chronic lung disease, it can also be associated with neoplasms of the chest, usually bronchogenic carcinoma. Five to ten percent of patients with bronchogenic carcinoma develop clubbing[93]. Mesothelioma can also produce similar changes. Clubbing can also be produced by other solid tumors metastatic to the thorax and has been reported in Hodgkin's disease of the lung. Clubbing can also be seen with diffuse intestinal lymphoma.

Peutz-Jeghers Syndrome

The association of cutaneous and mucosal hyperpigmentation with gastrointestinal tract polyposis is now well known[94,]. The skin hyperpigmented macules are usually present at birth or early infancy and frequently fade at puberty. They can be typically grouped around the mouth, eyes, and nostrils, with pigmented macules also located on

the fingers, palms, toes, periumbilical skin, or diffuse over the skin surface. Mucosal pigmented lesions are similar but persist for life.

The most common malignancy associated with the Peutz-Jeghers syndrome is duodenal carcinoma. These malignant tumors are frequently associated with hamartomatous polyps. The lifetime risk of a patient with Peutz-Jeghers syndrome developing an upper gastrointestinal tract malignancy carries an overall cancer relative risk of up to 18[94].

Tuberous Sclerosis

Tuberous sclerosis can be associated with tumors within many organ systems. Most of these are hamartomatous, and some of these can become malignant. However, malignant transformation in tuberous sclerosis is uncommon, occurring in probably no more than 5 percent of patients.

Multiple Eruptive Seborrhoeic Keratoses

Multiple eruptive seborrhoeic keratoses, also known as the sign of Leser- Trélat, have been mentioned in association with multiple internal malignancies[95]. These malignancies have included tumors of the stomach, breast, prostate, lung, and colon and malignant melanoma, as well as many references to their occurrence in lymphoma, primary lymphoma of the brain, and mycosis fungoides,

including Sézary syndrome. Evidence to support the presumed relationship of seborrheic keratoses to malignant disease is meager[96]. Most of the cancers described in association are common; seborrheic keratoses are common. Proving an uncommon causal relationship between a common cancer and a common skin sign is difficult.

Porphyria Cutanea Tarda

Porphyria cutanea tarda has been associated with the development of malignant tumors, predominantly of the liver. The relative risk of hepatocellular carcinoma in patients with porphyria cutanea tarda has been estimated as 61[97], a truly significant association. The porphyria cutanea tarda can predate or antedate the apparent development of the primary liver tumor.

DIRECT TUMOR INVOLVEMENT IN THE SKIN

Direct involvement of the skin by metastatic spread from a distant primary tumor is perhaps the most unquestioned marker for the internal malignancy. In a large review by Lookingbill et al[98] skin involvement was the first sign of cancer in 0.8 percent of systemic cancer patients. Of this group, approximately equal numbers had direct extension to the skin, local metastases, or distant skin metastases.

It may be a indication for recurrence with known primary. It may be a presenting lesion of an unsuspected malignancy . It usually occur on skin in the vicinity of affected organ.It is commonly seen in older age group.

Cancers that have the highest propensity to metastasize to the skin include melanoma (45% of cutaneous metastasis cases), breast (30%), nasal sinuses (20%), larynx (16%), and oral cavity (12%). Because breast cancer is so common, cutaneous metastasis of breast cancer is the most frequently encountered type of cutaneous metastasis in most clinical practices. Although some tumors are very common, they may not necessarily eventuate in metastasis in a manner that parallels their incidence in the overall population. For example, prostate cancer is very common, but cutaneous metastasis from prostate carcinoma is relatively uncommon.

Direct extension was most common in patients with breast and oral cancer. Local metastases were most common in patients with breast cancer or pelvic cancer. Distant metastases were from lung, colon, stomach, upper aerodigestive tract, uterus, kidney & lymphoma[3].

Generally such a metastatic lesion is obvious, being an erythematous cutaneous or subcutaneous mass, and is frequently

rapidly growing. At times, it can be difficult to diagnose metastatic lesions especially with metastases from breast cancer.

Carcinoma Breast

Most commonly breast cancer lesions metastasize to the anterior chest wall. They can typically show up as small nodules ranging from tiny 1- to 2- mm lesions to large masses of tumor. The tiny nodules can be erythematous or can be frankly hemorrhagic. The hemorrhage can be present within the nodules or in the field surrounding the nodules. The various morphologic variants of cutaneous metastases observed with Carcinoma breast are Carcinoma Erysipeloides(Inflammatory Carcinoma),Nodular metastatic carcinoma, En cuirasse metastatic Carcinoma, Carcinoma telangiectatica and Carcinoma of inframammary crease.

Paget's disease of the nipple is an erythematous scaling eruption that indicates ductal carcinoma of the underlying breast.

Lung Cancer

Lung cancer is the most common cause for cutaneous metastasis in men. The commonest site for cutaneous metastases in men is the chest, followed by the abdomen and the back. Other areas (in decreasing order of frequency) include the scalp, the neck, the face, the extremities, and the pelvis. For women, the most common

areas (in decreasing order of frequency) are the chest, the abdomen, the back, and the upper extremities.

Gastrointestinal cancers (usually colon and stomach cancer)

They often metastasize to the abdomen and the pelvis. Gastrointestinal carcinomas may spread along the urachus and produce nodules at the umbilicus. The presentation of nodules at the umbilicus has been referred to as a Sister Mary Joseph nodule. Sister Mary Joseph was a nurse at the Mayo Clinic who helped to prepare patients prior to operation for gastrointestinal surgery. She noted that the nodules at the umbilicus were an ominous sign of extensive involvement of colorectal carcinoma.

Malignant Melanoma

About 60,000 Americans develop malignant melanoma each year, but only 9000 deaths are attributed to malignant melanoma annually in the United States. When malignant melanoma metastasizes, the skin is commonly involved. In men, melanomas are likely to metastasize to the chest, the extremities, and the back. A large portion of female patients have metastases to the lower extremities. Metastases of melanoma may simulate blue nevi and may be epidermotropic or simulate primary cutaneous melanoma.

Neoplasm of Oral Cavity

Cutaneous metastases from squamous cell carcinoma in the oral cavity usually remain in the local area, most often affecting the neck and the face.

Renal Tumours

Renal cell carcinoma may metastasize to the scalp, to operative scars, or on many other surfaces. Because of the prominent vascular supply of renal cell carcinoma, lesions may mimic a hemangioma or a pyogenic granuloma, sometimes it can be pulsatile.

Neoplasm of Genital Tract

Metastases from the ovary and the uterus are seen in the skin of the lower abdomen, the groin, or the upper thigh.

Neoplasm of Endocrine glands

Metastases thyroid carcinoma may be pulsatile and may have a bruit.

Lymphoma-Leukemia

Involvement of the skin with lymphoma cells is quite common, particularly in the case of a T cell lymphoma[3]. T cell leukemias frequently have skin involvement, and this involvement may manifest itself as a diffuse erythroderma as is seen in Sézary syndrome.

B cell lymphomas can also involve the skin, with Hodgkin's disease being the most common. B cell lymphoma involvement of the skin is usually manifested by the development of one or more papules or nodules that may be ulcerated and form arcuate lesions. Alopecia can also be caused by lymphoma. Alopecia mucinosa is involvement of the hair follicles by lymphoma, with associated mucin deposition. Other lymphocytic, myeloid, and myelomonocytic leukemias can have cutaneous manifestations. The most common of these are the infiltrations of the skin produced by monocytic or myelomonocytic leukemia, which can produce a leonine facies in addition to other infiltrative plaques. Involvement of the skin can be a presenting feature in myelomonocytic leukemia, although it generally occurs late in the course of the disease. Multiple myeloma can appear as small red nodules on the skin surface with diagnostic myeloma histology.

Extra Mammary Paget's Disease

Extramammary Paget's disease, which can occur in the anogenital skin, similarly may be associated with an underlying adenocarcinoma. The underlying carcinoma may be of apocrine or eccrine sweat gland origin, or can be from the rectum or urethra[3].

AIM OF THE STUDY

1. To study the incidence of Cutaneous Manifestations in patients with internal Malignancy.

2. To study the age & sex predilection of Cutaneous Manifestations in patients with internal Malignancy.

3. To study the incidence of specific and non specific cutaneous manifestations in relation to various internal Malignancies

4. To study the clinical pattern of cutaneous manifestations among patients with internal malignancy.

5. To study the incidence of genodermatoses among patients of internal malignancy with cutaneous manifestations.

6. To study the prognostic significance of the cutaneous manifestations.

MATERIALS AND METHODS

A total number of 750 patients attending the Cancer Chemotherapy Out Patient Department and proven Cancer patients referred to Dermatology Out Patient Department for various skin problems were screened for cutaneous lesions.

The cancer patients attending the Dermatology O.P.D. were mainly referred from other departments like Hematology, Surgery and Gastro Enterology. Patients attending the cancer chemotherapy O.P.D. were mostly proven cases of malignancy. They were referred from other departments in Government General Hospital, Chennai and from other hospitals of the state and nearby states. Only those confirmed to be having a malignant disease were included. Those cases that proved to be negative for malignancy after investigation were excluded.

In patients who had skin lesions, the age, sex, duration of the primary neoplasm, the duration between the onset of primary neoplasm and the onset of cutaneous lesions, symptoms of cutaneous lesions and history of relapse were noted.

On clinical examination, importance was given to the features like the site of the cutaneous lesions, morphology of the lesion, the number and the arrangement and distribution of the lesions were

noted. Hematological, radiological and cytological investigations were done to confirm the site of primary neoplasm in some patients. Skin biopsy of the cutaneous lesions suggestive of Metastases was done for histopathological examination. Fine Needle aspiration Cytology was done in one case with neck secondary since the patient was very ill. In one case with Erythroderma, T-cell marker study was done. The skin surface was divided into nine regions as done by Brownstein et al[100] for recording the site of metastasis and the observations are tabulated as follows.

OBSERVATIONS AND RESULTS

- Total number of Cancer Patients screened – 750
- Total number of cases found to have Cutaneous Manifestations–52
- The incidence of cutaneous manifestations in this study –6.93%

Age & Sex Incidence

- The male female ratio in this study was 34: 18
- Percentage of Male patients with Skin lesions – 65.38
- Percentage of Female patients with Skin lesions – 34.62
- In males the youngest patient encountered was a 15 yrs old boy while the oldest patient was 75 yrs of age.
- In Females the Youngest patient encountered was a 14 yrs old girl while the oldest patient was 63 yrs of age

Sex	Number of cases	Percentage (%)
Male	34	65.38
Female	18	34.62
Total	52	100

Incidence of internal malignancy with skin manifestations

Lymphomas and leukemias were the commonest neoplasm producing cutaneous manifestations among all patients followed by Carcinoma Breast and Carcinoma Stomach. The other malignancies encountered in our study in descending order of frequency were Carcinoma Cervix, Carcinoma Prostate, Carcinoma Buccal Mucosa, Malignant Melanoma, Seminoma, Carcinoma Oesophagus, Carcinoma Pharynx, Hepato Cellular Carcinoma, Astrocytoma, Pheochromocytoma, Secondaries liver and neck with unknown primary.

Internal Malignancy		Number of cases	Percentage
Non Hodgkin's Lymphoma		10	19.2
Leukemia	ALL – 2	10	19.2
	AML – 3		
	CLL – 4		
	PCV – 1		
Carcinoma Breast		7	13.46
Carcinoma Stomach		6	11.5
Carcinoma Cervix		3	5.76
Carcinoma Prostate		3	5.76
Carcinoma Buccal Mucosa		3	5.76
Malignant Melanoma		2	3.84
Seminoma		1	1.92
Carcinoma Oesophagus		1	1.92
Carcinoma Pharynx		1	1.92
Hepatocellular carcinoma		1	1.92
Astrocytoma		1	1.92
Pheochromocytoma		1	1.92
Secondaries liver		1	1.92
Secondaries neck		1	1.92

Age predilection of Cutaneous Manifestations of Internal Malignancy

In males, the most patients belonged to 5th and 6th decade.

In females, the most patients belonged to 5th decade.

Age group	Male		Female	
	Number of cases	Percentage	Number of cases	Percentage
11-20	2	5.8	2	11.11
21-30	-	-	-	-
31-40	4	11.7	2	11.11
41-50	5	14.7	4	22.22
51-60	11	32.35	9	50.0
61-70	11	32.35	1	5.5
71-80	1	2.9	-	-
	34	100	18	100

Sex wise Incidence of Internal Malignancy with skin manifestations.

Non-Hodgkin's Lymphoma was the commonest Neoplasm producing skin lesions in Male followed by Leukemias and Carcinoma Stomach.

Internal Malignancy in Male		Number of cases	Percentage
Non Hodgkin's Lymphoma		9	26.47
Leukemia	ALL - 2	5	14.7
	AML - 1		
	CLL - 2		
Carcinoma Stomach		5	14.7
Carcinoma Prostate		3	8.82
Carcinoma Buccal Mucosa		3	8.82
Malignant Melanoma		2	5.88
Seminoma		1	2.94
Carcinoma Oesophagus		1	2.94
Carcinoma Pharynx		1	2.94
Hepatocellular carcinoma		1	2.94
Pheochromocytoma		1	2.94
Secondaries liver		1	2.94
Secondaries neck		1	2.94
Total		34	100

In Females, Carcinoma Breast was the commonest neoplasm producing skin lesions followed by Leukemias, Carcinoma Cervix, Non-Hodgkin's Lymphoma, Carcinoma Stomach and Astrocytoma in descending order of occurrence.

Internal Malignancy in Female		Number of cases	Percentage
Carcinoma Breast		7	38.88
Leukemia	AML - 2	5	27.77
	CLL - 2		
	PCV - 1		
Carcinoma Cervix		3	16.66
Non-Hodgkin's Lymphoma		1	5.55
Carcinoma Stomach		1	5.55
Astrocytoma		1	5.55
Total		18	100

Incidence of Cutaneous Manifestations among Internal Malignancy patients.

Cutaneous Metastases was the commonest skin manifestation among cancer patients followed by Infections especially Herpes Zoster. The other nonspecific cutaneous manifestations encountered in the present study, in the descending order of frequency were generalized pruritus, multiple eruptive seborrhoeic keratoses, Bullous disorders, Erythema Multiforme, Erythroderma, Flushing, Purpura, SLE, Pyoderma Gangrenosum, Insect Bite Allergy reactions and Lichenoid dermatitis.

The incidence of Cutaneous Metastases in this study is 2.66%.

The incidence of Non-Specific Cutaneous Manifestation is 4.26%.

Cutaneous Manifestation		Number	Percentage
Metastases	Contiguous - 6	20	38.46
	Non Contiguous - 14		
Infections	Herpes Zoster - 11	14	26.9
	Varicellosis - 1		
	Herpes Simplex - 1		
	Scabies - 1		
Generalized Pruritus		3	5.76
Multiple Eruptive Seborrhoeic Keratoses		3	5.76
Bullous disorders	Paraneoplastic Pemphigus - 2	3	5.76
	Bullous Pemphigoid - 1		
Erythema Multiforme		1	1.92
Erythroderma		1	1.92
Flushing		1	1.92
Purpura		1	1.92
Systemic Lupus Erythematosus		1	1.92
Pyoderma Gangrenosum		1	1.92
Miscellaneous	Exaggerated IBA lesions-2 (3.84%)	3	5.76
	Lichenoid Dermatitis- 1 (1.92%)		

Sex Predilection of Cutaneous Manifestations of internal malignancy

In both males and females, cutaneous metastases were the commonest presentation followed by Herpes Zoster infection. Non-contiguous spread is more common in males, whereas contiguous spread is more common in females.

Cutaneous Manifestations	Male	Female	Total
Metastases			
-Contiguous	2	4	6
-Non Contiguous	12	2	14
Infections			
-Herpes Zoster	6	5	11
-Herpes Simplex	1	0	1
-Varicellosis	1	0	1
-Scabies	1	0	1
Generalized Pruritus	2	1	3
Multiple Eruptive Seborrhoeic Keratoses	2	1	3
Bullous disorders			
-Paraneoplastic Pemphigus	2	0	2
-Bullous Pemphigoid	1	0	1
Erythema Multiforme	1	0	1
Erythroderma	1	0	1
Flushing	1	0	1
Purpura	0	1	1
Systemic Lupus Erythematosus	1	0	1
Pyoderma Gangrenosum	0	1	1
Miscellaneous:			
Exaggerated IBA lesions	0	2	2
Lichenoid Dermatitis	0	1	3

CUTANEOUS METASTASES

Contiguous metastases

Carcinoma Breast (66.6%) was the most common neoplasm producing Contiguous metastases to skin.

Malignancy	Metastases to
Carcinoma breast – 3 patients	Chest wall
Carcinoma breast®	Nipple®
Carcinoma Buccal Mucosa(L)	Cheek(L)
Amelanotic melanoma- Cheek®	Neck® and chest

NON- CONTIGUOUS METASTASES

Site of Non-Contiguous Metastases:

The commonest site involved in the descending order of occurrence was anterior chest wall followed by anterior wall of the abdomen, lower limb, neck, back, upper limb, face, pelvis and scalp. Single site was involved in 5 patients. Multiple sites were involved in 9 patients.

SITE OF INVOLVEMENT OF CUTANEOUS METASTASES

Internal Malignancy	Scalp	Face	Neck	Upper limb	Chest	Abdomen	Back	Pelvis	Lower limb	Multiple sites
AML						+				
CLL									+	
NHL		+	+	+	+	+	+	+	+	+
NHL					+					+
Liver 2'		+	+		+	+				+
Ca Stomach	+		+		+	+	+			
NHL				+	+	+	+	+	+	+
NHL					+					+
AML				+	+	+			+	+
Ca Pharynx						+	+		+	
NHL Relapse									+	+
Malignant Melanoma			+		+					
Ca Oesophagus		+	+		+	+	+	+		+
Ca Stomach	+	+		+	+					+
Total	2	4	5	4	10	8	5	3	6	9

Clinical Pattern of Cutaneous Metastases:

Skin colored nodule was the common clinical presentation of cutaneous metastases, followed by plaques, papules, ulcer and tumor in the descending order of occurrence.

PATTERN OF CUTANEOUS METASTASES

Internal Malignancy	Papule	Nodule	Plaque	Tumor	Ulcer	Colour
Contiguous Metastases						
Amelanotic Melanoma		+	+			E/S
Ca Buccal mucosa			+			S
Carcinoma Breast			+		+	S
Carcinoma Breast	+	+	+		+	S/E
Ca Breast	+	+			+	S/E
Ca Breast	+	+			+	S/E
Non-Contiguous Metastases						
AML			+			E
CLL			+			E
NHL			+			E
NHL	+	+				S
Liver 2'	+	+				S
Ca Stomach		+			+	S/E
NHL		+			+	S
NHL		+		+	+	S
AML	+	+				S
Ca Pharynx		+				S
NHL Relapse	+	+	+		+	S/E
Malignant Melanoma		+				S
Ca Oesophagus			+			Hyper Pig
Ca Stomach		+			+	S/E
Total	7	14	9	1	9	

S – Skin colored ; E – Erythematous ; Hyper pig – Hyper pigmented ;

Pattern of Herpes Zoster seen in malignancy patients:

Among 11 patients with Herpes Zoster, six patients had single dermatomal involvement, two patients had dissemination of Herpes Zoster and three patients had multidermatomal involvement.

Primary Malignancy	Sex	Segment involved	Duration of skin lesions	complications
Carcinoma Breast(L)	F	C4®	3-4 weeks	Keloid, PHN+
Carcinoma Breast(L)	F	T2,T3,T4	3-4 weeks	Hypertrophic scar+, PHN+
Carcinoma Breast®	F	C7	3 weeks	Nil
Carcinoma Cervix	F	L3	3 weeks	Hypertrophic scar+
Carcinoma Cervix	F	C2,C3,C4	3-4 weeks	PHN
Seminoma®	M	T4	3 weeks	PHN
Carcinoma Buccal mucosa(L)	M	T6	3 weeks	PHN
Carcinoma Prostate	M	Ramsay Hunt Syn & C2,C3,C4	3 weeks	PHN
Carcinoma Stomach	M	Cr.III-ophthalmic	3-4 weeks	Hypertrophic scar+, PHN
Non-Hodgkins's Lymphoma	M	C2 with Dissemination	4-5 weeks	Hypertrophic scar+
CLL	M	T5 with Dissemination	4-5 weeks	Hypertrophic scar+

PHN – Post Herpetic Neuralgia

Various presentations of Internal Malignancy

Leukemia:

Leukemias had manifested with variety of skin lesions like cutaneous metastases, purpura, pruritus, pyoderma Gangrenosum, Photosensitivity, herpes Zoster, Varicellosis and exaggerated insect bite allergy lesions.

Skin Manifestations	Number of patients	Percentage
AML Purpura - 1 Non-Contiguous Metastases - 2	3	30
CLL Non-Contiguous Metastases - 1 Ex.IBA - 1 Pyoderma Gangrenosum - 1 Herpes Zoster - 1	4	40
ALL Varicellosis - 1 SLE - 1	2	20
PRV Pruritus	1	10
Total	10	100

Non-Hodgkin's Lymphoma: Non-contiguous Metastases was the common presentation encountered in patients with Lymphomas.

Deleted: ¶
¶

Skin Manifestations	Number of patients	Percentage
Metastases Non-Contiguous	5	50
Infections Herpes Zoster -1 Herpes Simplex -1	2	20
Paraneoplastic Pemphigus	1	10
Erythroderma	1	10
Erythema Multiforme	1	10
Total	10	100

Carcinoma Breast:

Carcinoma Breast manifested most commonly as Contiguous metastases followed by Herpes zoster infections.

Skin Manifestations	Number of patients	Percentage
Contiguous Metastases	4	57
Infections:- Herpes Zoster	3	43
Total	7	100

Carcinoma Stomach

Multiple Eruptive Seborrhoeic Keratoses and non-contiguous cutaneous metastases were the common cutaneous manifestations of Carcinoma stomach followed by Herpes Zoster infection and pruritus.

Skin Manifestations	Number of patients	Percentage
Multiple Eruptive Seborrhoeic Keratoses	2	33.33
Non-Contiguous Metastases:	2	33.33
Herpes Zoster	1	16.6
Pruritus	1	16.6
Total	6	100

Carcinoma Cervix

Carcinoma Cervix manifested most commonly with Herpes Zoster infection followed by exaggerated insect bite allergy lesions.

Skin Manifestations	Number of patients	Percentage
Herpes Zoster	2	66.66
Exaggerated IBA	1	33.33
Total	3	100

Carcinoma Buccal Mucosa

Skin Manifestations	**Number of patients**	**Percentage**
Contiguous Cutaneous metastases	1	33.33
Herpes Zoster	1	33.33
Scabies	1	33.33
Total	3	100

Carcinoma Prostate

Skin Manifestations	**Number of patients**	**Percentage**
Herpes Zoster	1	33.33
Bullous Pemphigoid	1	33.33
Multiple Eruptive Seborrhoeic keratoses	1	33.33
Total	3	100

Follow Up

Case No.	Skin Manifestations	Primary Neoplasm	Period of Survival after the onset of cutaneous manifestations in months.	Follow up
	Cutaneous Metastases			
30	Contiguous Metastases	Amelanotic melanoma	12/12	Alive
31	Contiguous Metastases	Ca Buccal mucosa	7/12	LTF
32	Paget's disease of Nipple	Carcinoma Breast	8/12	LTF
33	Contiguous Metastases	Carcinoma Breast	5/12	LTF
34	Contiguous Metastases	Ca Breast	4/12	Died*
35	Contiguous Metastases	Ca Breast	6/12	Died*
36	Non-Contiguous Metastases	AML	8/12	LTF
37	Non-Contiguous Metastases	CLL	12/12	Alive
38	Non-Contiguous Metastases	NHL	12/12	Alive
39	Non-Contiguous Metastases	NHL	10/12	Alive
40	Non-Contiguous Metastases	Liver 2'	3/12	Died*
41	Non-Contiguous Metastases	Ca Stomach	4/12	LTF
42	Non-Contiguous Metastases	NHL	4/12	Died*
43	Non-Contiguous Metastases	NHL	5/12	LTF
44	Non-Contiguous Metastases	AML	3/12	LTF
45	Non-Contiguous Metastases	Ca Pharynx	4/12	Died*
46	Non-Contiguous Metastases	NHL Relapse	2/12	Died*
47	Non-Contiguous	Malignant	6/12	Died*

	Metastases	Melanoma		
48	Non-Contiguous Metastases	Ca Oesophagus	6/12	Alive
49	Non-Contiguous Metastases	Ca Stomach	6/12	Alive
	Non-Specific Manifestations			
1	flushing	Pheochromocytoma	4/12	LTF
2	Purpura	AML	4/12	LTF
3	Bullous Pemphigoid	Ca Prostate	12/12	Alive
4	Paraneoplastic Pemphigus	2' Neck	6/12	Died *
5	Pemphigus vulgaris	NHL	8/12	Died*
6	Erythema Multiforme	NHL	12/12	Alive
7	H.zoster c3	Ca Breast (b/l)	12/12	Alive
8	H.zoster T1L3	Ca Breast	3/12	LTF
9	H.zoster C78	ca Breast	12/12	Alive
10	H.zoster L3	Ca Cervix	2/12	LTF
11	H.zoster IIICN	Ca Cervix	2/12	LTF
12	H.zoster T3	Seminoma ®	12/12	Alive
13	H.zoster T4	Ca Buccal mucosa	3/12	LTF
14	H.zoster RAMSAY	Ca Prostate	6/12	LTF
15	H.zoster IIICN	Ca Stomach	5/12	Died*
16	H.zoster DISSEM	NHL	4/12	LTF
17	H.zoster DISSEM	CLL	3/12	Died*
18	Herpes simplex labialis	NHL	12/12	Alive
19	Varicellosis	ALL	2/12	LTF
20	Scabies	Ca Buccal mucosa	8/12	Alive
21	Erythroderma	Sezary syndrome	12/12	Alive
22	SLE	ALL	4/12	LTF
23	Pruritus	Ca Stomach / 2' liver	2/12	Died*
24	Pruritus	HCC	14/365	Died*
25	Pruritus	PCV	6/12	LTF
26	Seb.keratoses	Ca Stomach	4/12	LTF
27	Seb.keratoses	Ca Prostate	6/12	LTF
28	Seb.keratoses	Ca Stomach	5/12	LTF
29	Pyoderma gangrenosum	CLL	8/12	LTF
50	Ex. IBA	CLL	5/12	LTF
51	Ex.IBA	Ca Cervix	8/12	Alive
52	Lichenoid dts	Astrocytoma	8/12	Alive

DISCUSSION

In this prospective study of 750 patients with internal malignancy, skin changes were found in 52 patients(6.93%) which is lower than that of study by Rajagopal et al[5](23%). This difference could due to the inclusion of Pediatric cases and cases having therapy induced skin changes in the later mentioned study.

Among 52 patients showing skin changes, 34 patients were males (65%) and 18 patients were females (35%). Similar male preponderance was also noted in a study by Rajagopal et al[5].

65% of male patients belonged to the age group of 50-70 yrs. More than 50% of female patients belonged to the group of 50-60 yrs as in Rajagopal et al[5] study. Cutaneous manifestations of internal malignancy can arise at any age. However, in keeping with the increased incidence of malignant disease in later life, most cutaneous manifestations occurred during or after the fifth decade.

In males the youngest patient encountered was a 15 yrs old boy, a case of ALL while the oldest patient was 75 yrs of age, a case of Carcinoma Prostate In Females the Youngest patient encountered was a 14 yrs old girl, a case of AML while the oldest patient was 63 yrs of age a case of Carcinoma Breast.

In our study, Metastases was the commonest skin lesion among malignancy patients with 38.46% followed by Herpes Zoster infection with 27%. The other nonspecific cutaneous manifestations encountered in the present study, in the descending order of frequency were generalized pruritus, multiple eruptive seborrhoeic keratoses, Bullous disorders, Erythema Multiforme, Erythroderma, Flushing, Purpura, SLE, Pyoderma Gangrenosum, Insect Bite Allergy reactions and Lichenoid dermatitis.

The internal malignancies with cutaneous manifestations in present study were Leukemia (19%), Lymphoma (19%), Carcinoma Breast (13.46%) and Carcinoma Stomach (11.5%). The less frequent causes were Carcinoma Cervix, Carcinoma Prostate, Carcinoma Buccal Mucosa, Secondaries neck and liver with unknown primary neoplasm, Seminoma, Hepato Cellular Carcinoma, Astrocytoma and Pheochromocytoma.

According to the literature, genodermatoses account for a minority of paraneoplastic skin lesions. In contrast, in our study, none of the patients had features of associated Geno-Dermatoses.

Cutaneous Metastases:

Cutaneous Metastases formed almost 1/3rd of total cases (38.46%).

The incidence of Cutaneous Metastases in this study was 2.66%, which is more than that of Tharakaram Study[99] (1.4%).

The incidence of Non-Specific Cutaneous Manifestation was 4.26%.

According to the literature[3], the most common internal malignancies to give rise to cutaneous metastases are carcinomas of the lung and colon in males and carcinoma of the colon and ovary in females. Overall, melanomas are the commonest followed by carcinoma breast, carcinomas of oral cavity, lungs, colon and ovary. However in our study, Non-Hodgkin's lymphoma was the commonest neoplasm to produce cutaneous metastases followed by Carcinoma breast, and leukemias.

Non contiguous Metastases was more common in males (85%) than females (15%), and contiguous spread was more commonly encountered in females (66.6%) than males (33.3%). This difference could be because the malignancy encountered in both sexes was different.

The period of interval between the onset of symptoms of the primary malignancy and onset of cutaneous metastases ranged from 2 months to 5 years. The shortest duration was 2 months in a case of

AML and the longest time interval was 5 years in a case of Carcinoma breast.

In present study, Carcinoma Breast was the commonest (66%) neoplasm causing direct extension to the skin which corroborates with the literature[3] followed by Carcinoma Buccal Mucosa and Amelanotic Melanoma.

Among 4 patients of Carcinoma Breast with contiguous metastases, three had recurrence and developed multiple skin colored and erythematous papules and nodules. Another Carcinoma Breast patient presented with ulcerative plaque over ®nipple and areola with history of bleeding and diagnosis of malignancy was possible by biopsy in that patient.

Non-Hodgkin's Lymphoma (35.7%) was the commonest neoplasm to produce non-Contiguous Metastases followed by Gastro-intestinal Malignancies (28.5%) and leukemias with (21.4%) especially AML Type. Others like Malignant Melanoma, and Secondaries liver and neck with unknown primary constitute 7% each.

In this study, the commonest site of metastases was the anterior chest wall followed by the anterior abdominal wall which corroborates with the similar finding observed in the studies by Tharakaram et al[99], Brownstein et al[100] and Rajagopal et al[5].

In our study, Skin colored nodule is the commonest clinical presentation of distant metastases and most often occurred in multiple sites which corroborates with the study by Rajagopal et al[5]. We also encountered plaques, papules, ulcers and tumor in the descending order of frequency. Erythematous papules, nodules and plaques, and pigmented plaques were also noted in the present study.

Non-Specific Skin Manifestations associated with Internal Malignancy:

Among non-specific lesions associated with internal malignancies, Infection particularly Herpes Zoster stood first with (27%), in contrast, Herpes zoster stood second in the study by Rajagopal et al[5].

Carcinoma Breast (27%) was the commonest Malignancy associated with Herpes Zoster and Carcinoma Cervix (18%) stood second.

Among 11 patients with Herpes Zoster, six patients had single dermatomal involvement, two patients had dissemination of Herpes Zoster and 3 patients had multidermatomal involvement. Among six patients with single dermatome involvement, one patient had Herpes Zoster Ophthalmicus and the remaining five patients had single dermatome involvement (C4,C7, T4, T6 and L3). One patient had

involvement of Geniculate Ganglion (Ramsay Hunt Syndrome) with involvement of C2,C3 & C4. Healing time was prolonged in 6 patients. Post Herpetic Neuralgia was the commonest complication found in these patients which corroborates with the study by Shanbrom et al[102] .

According to literature[3], the dermatomal distribution of the herpes zoster may indicate involvement of the nerve root area with Carcinoma Breast metastases. In contrast, In this study, none of the patients developed any feature of metastases in the dermatomal distribution during the study period.

According to literature[3], disseminated herpes zoster is commonly associated with underlying malignant disease like lymphoma and leukemia. Which is consistent with our study and two of our patients with Disseminated Herpes Zoster lesions had NHL and CLL. We also encountered an ALL patient with Varicellosis of prolonged duration and a Non Hodgkin's Lymphoma patient with recurrent Herpes Simplex Labialis infection.

We also encountered Scabies infection in a patient with Carcinoma Buccal Mucosa.

In present study, we encountered Paraneoplastic Pemphigus in two patients. One of the patients was having Non-Hodgkin's Lymphoma which was found to be commonly associated neoplasm

with Paraneoplastic Pemphigus in a study by Anhalt et al[101]. Another patient developed Paraneoplastic Pemphigus lesion which preceded the neck Secondary by 3 months. In this patient, FNAC of neck secondary showed atypical squamous cells. Both the patients with paraneoplastic pemphigus lesions expired.

One of our patient with Carcinoma Prostate developed bullous pemphigoid lesions which is also reported in literature[4].

According to literature[3], Erythema Multiforme appears to occur more frequently with Acute Leukemias. In present study, a patient with NHL having Erythema Multiforme over chest, abdomen and extremities was encountered. It is hard to evaluate, whether it occurred as reaction to drugs, radiotherapy or associated infections.

In present study, pruritus was noticed in 3 patients with Hepatocellular carcinoma, Polycythemia Vera and Carcinoma Stomach. Pruritus was observed as a common manifestation among internal malignancy patients in the study by RajaGopal et al[5].

The patient with Hepatocellular carcinoma developed generalized intractable itching along with jaundice, not responding to conventional antihistamines and USG abdomen helped to diagnose the condition.

Among other two patients with generalized prirotus, one had Polycythemia Rubra Vera and another patient had Carcinoma Stomach with liver Secondaries.

In present study Multiple Eruptive Seborrhoeic Keratoses (MESKs) was seen in three patients. In our study, Carcinoma Stomach (66.66%) was the most common primary neoplasm associated with MESKs which corroborates with the literature[3], followed by Carcinoma Prostate.

Seborrhoeic keratoses are extremely common in normal population also. Proving an uncommon causal relationship between a common cancer and a common skin sign was difficult as the number of patients in this study were few.

In an elderly male with Sezary Syndrome with erythroderma and generalized lymphadenopathy, the diagnosis was made by Peripheral smear and T cell marker study.

In this study, we encountered a patient having pronounced flushing involving the central face and upper trunk for the past 2 months which led to the diagnosis of Pheochromocytoma.

A known case of AML, presented with multiple purpuric spots over the abdomen, thighs and legs. Acute leukemias are mentioned as a cause of Purpura in the literature.

According to literature[3], Systemic Lupus Erythematosus is only rarely associated with malignant Neoplasia, most often with lymphoma or thymoma. In contrast, in the present study, SLE was found in association with ALL.

In a woman with Pyoderma gangrenosum associated with CLL, morphology was that of ulcerative type in contrast to bullous type reported in literature[3].

In present study, exaggerated insect bite allergy reactions were noted in two female patients with malignancy like CLL and Carcinoma Cervix. It is still not clear, whether the immunological imbalance occurring in leukemic patients or the radiotherapy induced immunological instability is responsible for such exaggerated insect bite allergy lesions.

In present study, a patient having Astrocytoma in ® thalamus region developed diffuse lichenoid dermatitis throughout the body within a period of 2 months duration. The lesions were more prominent over exposed parts.

Prognostic Significance of Cutaneous Manifestations of Internal Malignancy

The prognostic Significance of the Cutaneous Manifestations depends on various factors, whether the Manifestation is specific or

non specific, the type of internal Malignancy, the mode of interventional therapy and the general immune status of the patient.

In our study of cutaneous manifestations with internal Malignancy,

23 out of 52 Patients (44%) were lost for follow up. In the remaining 29 patients, 13 patients (44%) succumbed to their illness.

7 patients (54%) showing Specific cutaneous metastases expired. Whereas, 6 patients (37%) showing non specific Cutaneous Metastases expired.

Cutaneous Metastases:

In our study, 20 out of 52 patients had Cutaneous Metastases. 7 patients(54%) showing Specific cutaneous metastases expired in the period ranging from 2-6 months.

The shortest survival period (2 months) was seen in a patient who developed recurrence of NHL. Two out of the three patients with Carcinoma Breast, who developed recurrence of malignancy after surgery, expired in 4 months and 6 months respectively.

Except for a patient with NHL relapse, many patients with Cutaneous Metastases survived for a minimum of 3 months, which corroborates with the study by Reingold.

Non-Specific Cutaneous Manifestations:

The casual relationship between the Non Specific Cutaneous Manifestation and the internal malignancy is very difficult to prove. It depends mainly on the type of cutaneous manifestation involved and the internal malignancy under study. This was because some cutaneous Manifestations are common especially Herpes Zoster & Seborrhoeic keratoses, and some malignancies were more common like NHL, Leukemias & Carcinoma Breast. Similarly Survival Period is also difficult to assess based on Non-Specific Cutaneous Manifestation of Internal Malignancy.

6 (37%) showing non specific Cutaneous Metastases expired in the period ranging from 14 days to 8 months. The Shortest Survival (14 days) was noted in a patient with Hepatocellular Carcinoma. Both Paraneoplastic Pemphigus expired with in 6 months and 8 months respectively. A CLL patient with Disseminated Herpes Zoster also Succumbed to the illness with in 3 months.

Cutaneous Metastases, indicating a sign of recurrence, and wide spread metastases had poor prognosis and survival period is reduced when compared to others.

Among Non-specific manifestations, the Bullous disorders and disseminated Infections had poor prognosis.

CONCLUSION

1. The incidence of Cutaneous Manifestations associated with internal malignancy is 6.93%

2. Out of 52 patients having cutaneous Manifestations with internal Malignancy, 34 patients were Male (65%) and 18 were female (35%). Males and Females above 50 yrs had more cutaneous Manifestations associated with internal Malignancy.

3. The incidence of Cutaneous Metastases in this study was 2.66%, and the incidence of Non-Specific Cutaneous Manifestation was 4.26%.

4. Lymphomas and Leukemias were the commonest neoplasm producing cutaneous manifestations followed by Carcinoma Breast and Carcinoma Stomach. Cutaneous Metastases was the commonest skin manifestation among Malignancy patients followed by Herpes Zoster.

   Non-Contiguous Metastases was more common in males whereas Contiguous Metastases was more common in females.

   The period of interval between the onset of symptoms of the primary malignancy and onset of cutaneous metastases ranged from 2 months in a case of AML to 5 years in a case of Carcinoma Breast. Contiguous Cutaneous Metastases was more commonly seen with Carcinoma Breast and Non-

Hodgkin's Lymphoma was the commonest neoplasm to produce non-Contiguous Metastases.

Skin colored nodule was the commonest clinical presentation of cutaneous metastases and most often occurred in multiple sites, The commonest site of distant Metastases was Chest, followed by abdomen and lower limb. Leukemias had manifested with variety of skin lesions like cutaneous metastases, purpura, pruritus, pyoderma gangrenousm, Systemic lupus erythematosus, herpes Zoster, Varicellosis and exaggerated insect bite allergy lesions. Dissemination, Multidermatomal involvement, longer healing time, tendency for Keloid formation and Post Herpetic Neuralgia was observed in Malignancy patients with Herpes Zoster.

5. Genodermatoses with associated internal malignancy was not noted.

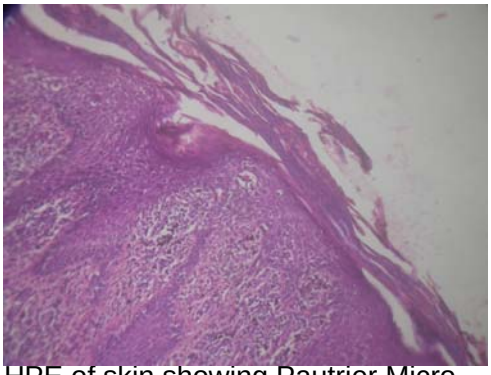
6. Cutaneous metastases indicating recurrence of NHL and Carcinoma Breast, the survival period was 2 months and 6 months respectively. Among cases of Non-Specific cutaneous manifestation, the shortest period of survival was 14 days in a case of HepatoCellular Carcinoma.

The prognosis could not be definitely ascertained because of small number of cases studied and the large number of drop outs, but in general Cutaneous Metastases, the Bullous disorders and disseminated Infections had poor prognosis.

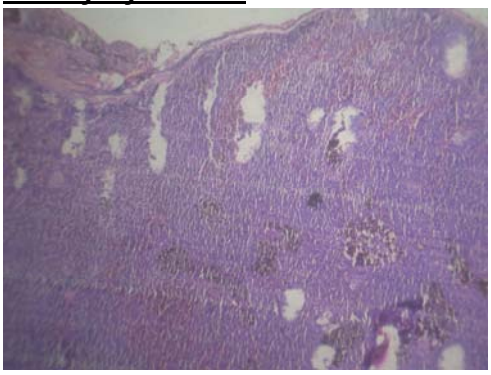
Sezary Syndrome

Non – Hodgkin's Lymphoma with Sezary Syndrome showing diffuse Erythroderma, Hyperkeratoses on palms and soles and dystrophic nails.

Sezary Syndrome



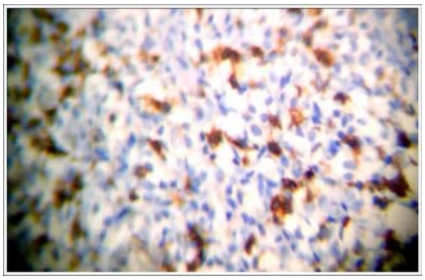
HPE of skin showing Pautrier Micro abcess in epidermis and epidermo tropism of atypical lymphocytes.



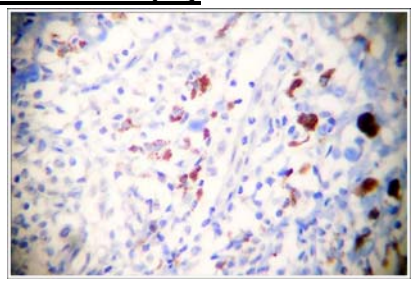
HPE of lymphnode showing widening of interfollicular areas and foamy, pigment laden Macrophages

.

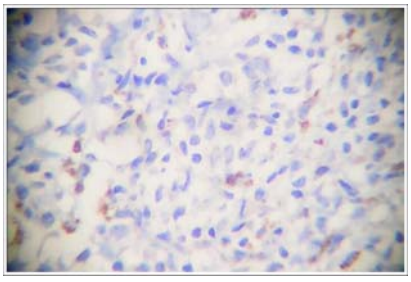
Immuno Histo Chemistry of skin biopsy



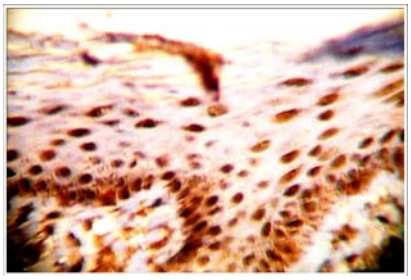
CD 3 Positive



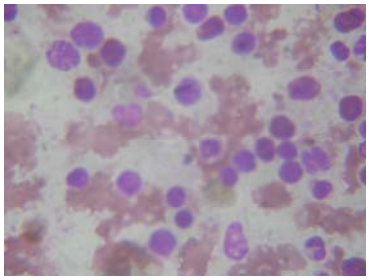
CD 4+ Positive



CD 43 Positive



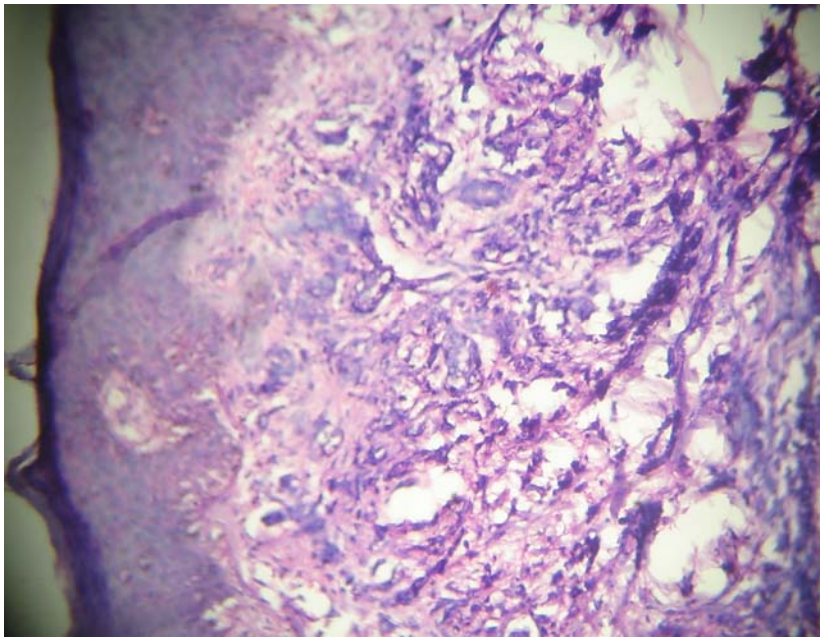
CD 30 Negative



Peripheral Buffy coat smear showing Sezary Cells

Metastatic Breast Carcinoma

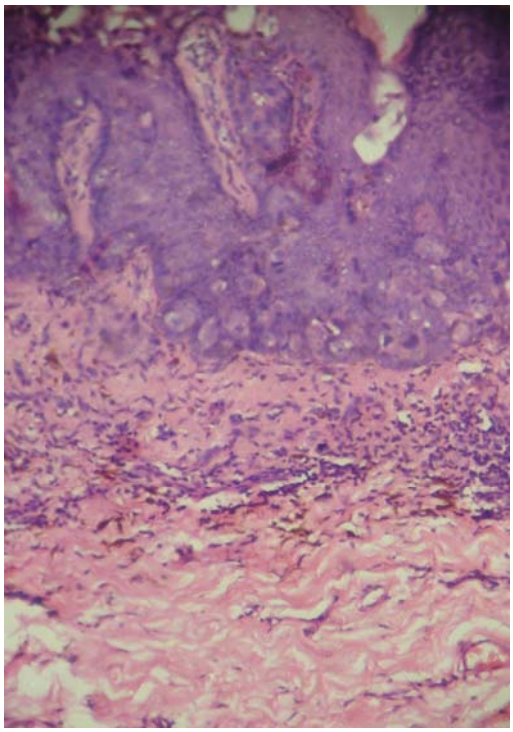
Metastatic Breast Carcinoma showing multiple papules, nodules and ulcer over anterior chest wall



Metastatic Breast Carcinoma showing loops and rows of polyhedral cells with hyperchromatic and pleomorphic nuclei, and occasional areas of glandular formation

Paget's Disease of Nipple

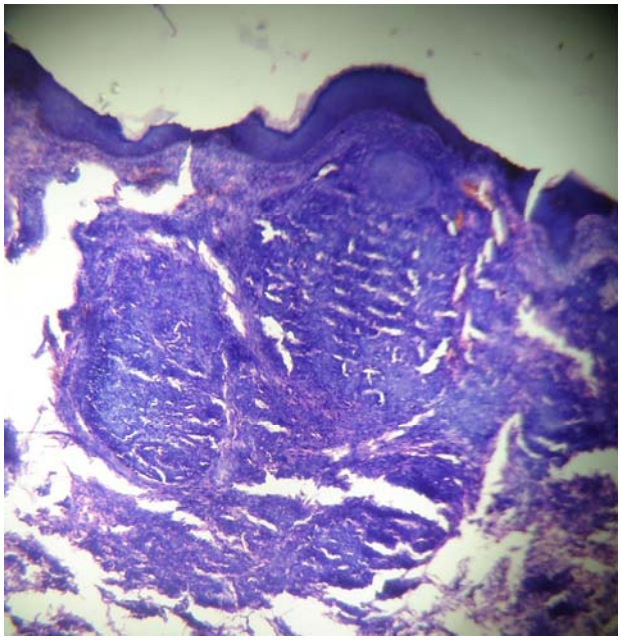
Carcinoma Breast with ulcerative plaque over nipple and areola, and retraction of the nipple



Metastatic Breast Carcinoma showing Pagetoid cells in the Epidermis

Metastatic Stomach Carcinoma

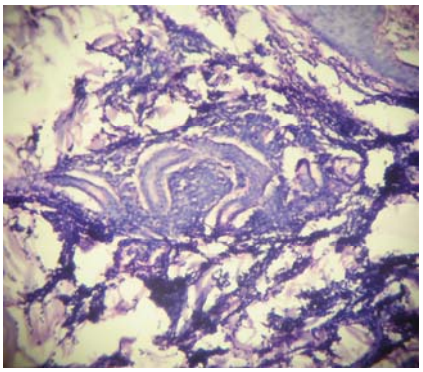
Metastatic Stomach Carcinoma showing Erythematous nodule over the neck



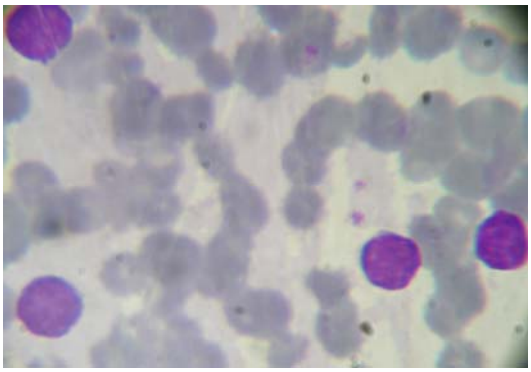
Metastatic Stomach Carcinoma showing collection of atypical epithelial cells in the upper dermis

Leukemic Deposits

Metastatic CLL showing infiltrated plaque over right thigh



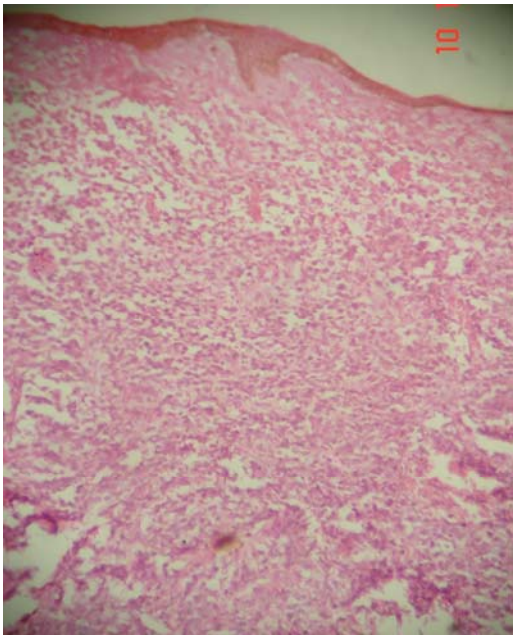
HPE showing clusters of lymphoid cells around skin appendages and subcutaneous tissue



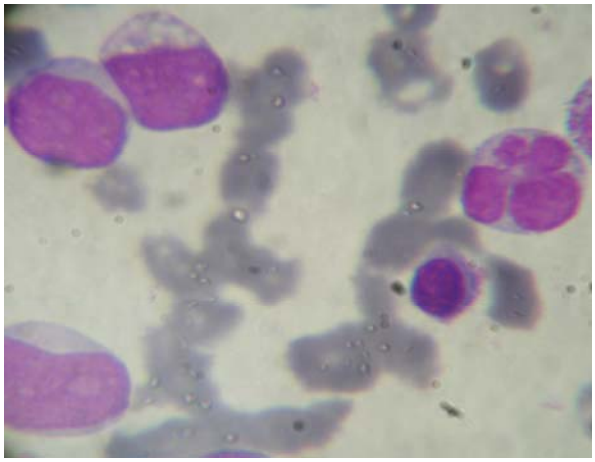
Peripheral smear of CLL showing mature and large lymphocytes

Lymphomatous Deposit

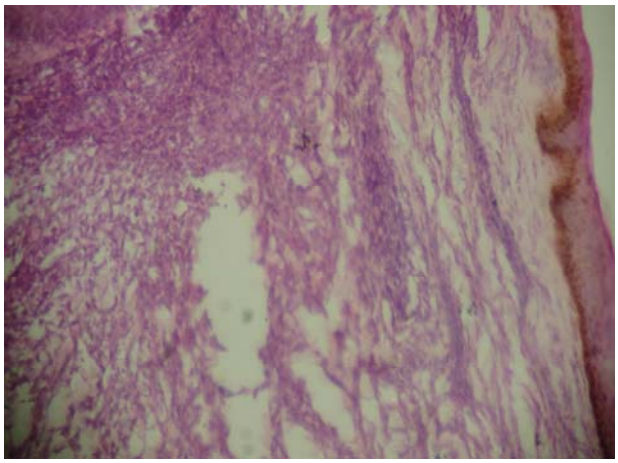
Metastatic Non Hodgkin's Lymphoma with multiple plaques over the neck



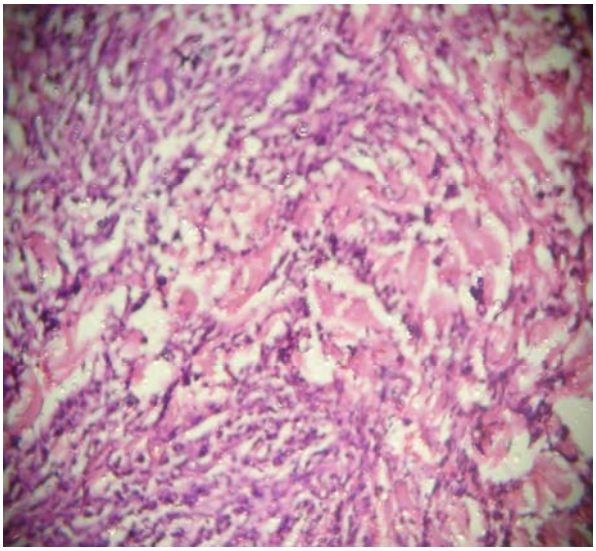
Metastatic Non Hodgkin's Lymphoma showing diffuse sheets of monotonus appearing round cells



Peripheral smear of AML showing Myeloblasts and nucleated RBC’s



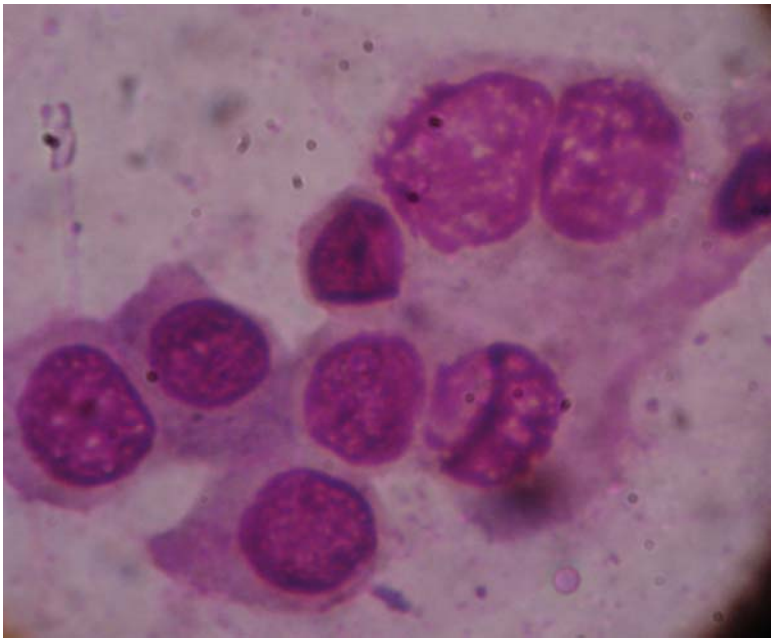
Metastatic AML showing Myeloid deposits around adnexal structures



Metastatic Carcinoma Pharynx showing Malignant epithelial cells in diffuse and nodular pattern and separating the fibrous tissue.

Herpes Zoster

Carcinoma Stomach with Herpes Zoster Ophthalmicus



Tzanck Smear of Herpes Zoster showing Multinucleated Giant Cells

Herpes Zoster

Seminoma with Herpes Zoster(T4)

Carcinoma Cervix with Herpes Zoster (C2,C3,C4)

Herpes Zoster

Carcinoma Prostate with Ramsay hunt Sundrome. Patient had Lagopthalmos, deviation of angle of mouth, obliteration of left side nasal labial furrow and herpes zoster infection involving C2,C3 & C4.

Keloid formation in Post Herpetic infection scar in a patient with Carcinoma Breast

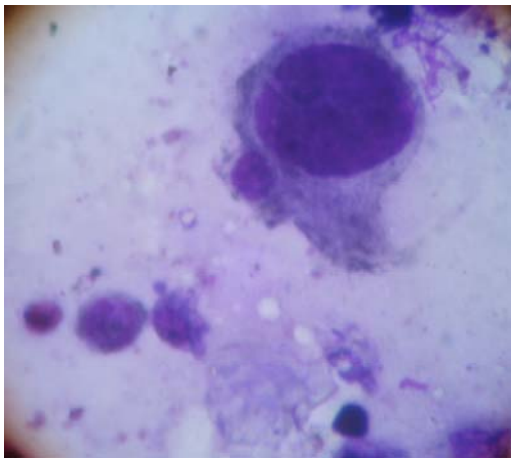
ALL patient with Varicellosis

Carcinoma Buccal Mucosa with Scabies Infection

Paraneoplastic pemphigus

Neck Secondaries with Paraneoplastic Pemphigus lesion

Paraneoplastic Pemphigus showing severe Oral erosions



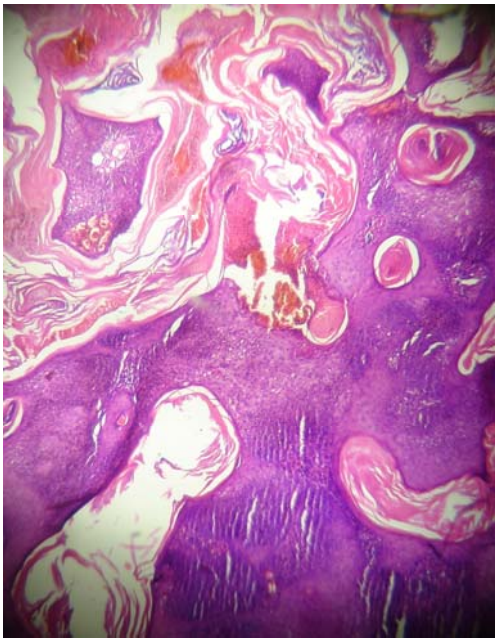
Tzanck smear showing Acantholytic cell

Carcinoma Prostate with Bullous Pemphigoid showing tense bulla over the abdomen and ruptured blister over the chest

CLL with Pyoderma Gangrenosum over ® thigh and ® leg.

Pheochromocytoma with flushing over face and upper chest.and was blanchable

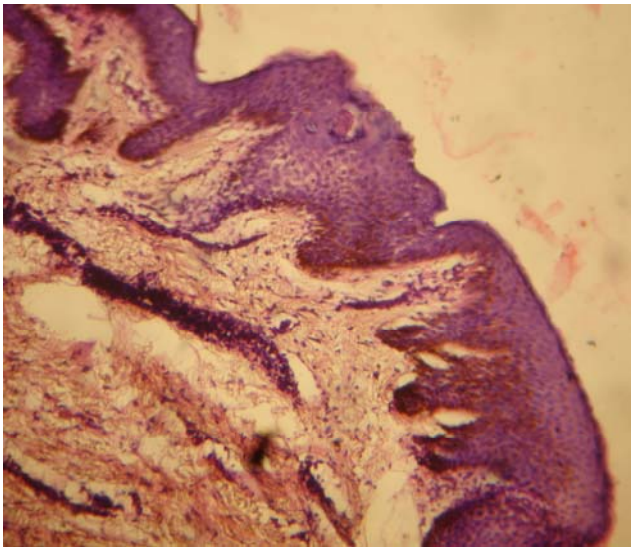
Carcinoma Stomach with liver Secondaries having Icterus and generlaised excoriations marks



Carcinoma Stomach with Multiple Eruptive Seborrhoeic Keratoses over face, trunk and upper arms. HPE showed Hyperkeratoses and numerous horn cysts.

Carcinoma Cervix with Exaggerated Insect Bite Allergy lesions involving flexor and extensor surfaces of forearms.


Astrocytoma with lichenoid dermatitis involving extremities and flexures



HPE of lichenoid dermatitis showed irregular acanthosis, basal cell degeneration and lymphocytic infiltrate in the upper dermis

ALL patient with Photosensitivity(SLE)

Non Hodgkin’s Lymphoma having skin colored nodules over chest and abdomen

Metastatic carcinoma stomach with ulcerative nodule over (L) shoulder

Amelonotic Melanoma over right cheek with multiple erythematous and skin colored nodules and papules over the neck.

BIBLIOGRAPHY

1. Gates O. Cutaneous metastses of malignant disease Am J Der. vol.30, p 718 - 730, 1937.

2. Brownstein M H, Helwig E B : Spread of tumours to the skin. Archives of Dermatology vol.107, p 80 - 86, Jan 1973.

3. Fitz Patrick's Dermatology in General Medicine, sixth edition,Vol.2, p1783-1796, 2003.

4. Rook's textbook of Dermatology, seventh edition, Vol.3;59.22-59.23, 2004.

5. Rajagopal R, Arora PN, Ramasastry CV, Kar PK. Skin changes in internal malignancy. Indian J Dermatol Venereol Leprol 2004;70: 221-5.

6. Nelson DH et al: ACTH-producing pituitary tumors following adrenalectomy for Cushing's syndrome. Ann Intern Med 52:560, 1960.

7. Andreev VC, Petkov I: Skin manifestations associated with tumours of the brain. Br J Dermatol 92:675, 1975.

8. Powell LW, Isselbacher KJ: Hemochromatosis, in Harrison's Principles of Internal Medicine, 14th ed, edited by AS Fauci et al.New York, McGraw-Hill, 1998, p 2149.

9. Lynch PJ, Winkelmann RK: Generalized plane xanthoma and systemic disease. Arch Dermatol 93:639, 1966.

10. McCadden ME et al: Mycosis fungoides associated with dystrophic xanthomatosis. Arch Dermatol 123:91, 1987.

11. Cooper PH et al: Association of juvenile xanthogranuloma with juvenile myeloid leukemia. Arch Dermatol 120:371, 1984.

12. Maize JC et al: Xanthoma disseminatum and multiple myeloma. Arch Dermatol 110:758, 1974

13. Gertz MA, Kyle RA: Acute leukemia and cytogenetic abnormalities complicating melphalan treatment of primary systemic amyloidosis. Arch Intern Med 150:629, 1990.

14. Aldrich LB et al: Distinguishing features of idiopathic flushing and carcinoid syndrome. Arch Intern Med 148:2614, 1988.

15. Umeki S et al: Harlequin syndrome (unilateral flushing and sweating attack) due to spinal invasion of the left apical lung cancer (in Japanese). Rinsho Shinkeigaku 30:94, 1990.

16. Rosenbaum FF et al: Essential telangiectasia, pulmonic and tricuspid stenosis, and neoplastic liver disease: A possible new clinical syndrome. J Lab Clin Med 42:941, 1953.

17. Morrell D et al: Mortality and cancer incidence in 263 patients with ataxia-telangiectasia. J Natl Cancer Inst 77:89, 1986.

18. Swift M et al: Breast and other cancers in families with ataxia-telangiectasia. N Engl J Med 316:1289, 1987.

19. French AJ, Lilleyman JS: Bleeding tendency of T-cell lymphoblastic leukemia. Lancet 2:469, 1979.

20. Cairns SA et al: Squamous cell carcinoma of bronchus presenting with Henoch-Schönlein purpura. Br Med J 2:474, 1978.

21. Lacour JP et al: Cutaneous vasculitis and renal cancer: Two cases. Am J Med 94:104, 1993.

22. Greer JM et al: Vasculitis associated with malignancy. Medicine(Baltimore) 67:220, 1988.

23. Hughes GRV et al: Polyarteritis nodosa and hairy-cell leukemia. Lancet 1:678, 1979.

24. Gerber MA et al: Periarteritis nodosa, Australia antigen and lymphatic leukemia. N Engl J Med 286:14, 1972.

25. Palmer HM: Digital vascular disease and malignant disease. Br J Dermatol 91:476, 1974.

26. Fagrell B, Mellstedt H: Polycythemia vera as a cause of ischemic digital necrosis. Acta Chir Scand 144:129, 1978.

27. Lindelöf B et al: Pemphigoid and cancer. Arch Dermatol 126:66, 1990.

28. Ogawa H et al: The incidence of internal malignancies in pemphigus and bullous pemphigoid in Japan. J Dermatol Sci 9:136, 1995.

29. Sood VD, Pasricha JS: Pemphigus and Hodgkin's disease. Br J Dermatol 90:575, 1974.

30. Stillman MA, Baer RL: Pemphigus and thymoma. Acta Derm Venereol (Stockh) 52:393, 1972.

31. Vetters JM et al: Pemphigus vulgaris and myasthenia gravis. Br J Dermatol 88:437, 1973.

32. Safai B et al: Pemphigus vulgaris associated with a syndrome of immunodeficiency and thymoma: A case report. Clin Exp Dermatol 3:129, 1978.

33. Imamura S et al: Pemphigus foliaceus, myasthenia gravis, thymoma and red cell aplasia. Clin Exp Dermatol 3:285, 1978.

34. Anhalt GJ et al: Paraneoplastic pemphigus: An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 323:1729, 1990.

35. Sigurgeirsson B et al: Risk of lymphoma in patients with dermatitis herpetiformis. BMJ 308:13, 1994.

36. Dupont C: Herpes gestationis with hydatidiform mole. Trans St John's Hosp Dermatol Soc 60:103, 1974.

37. Halkier-Sorensen L et al: Herpes gestationis in association with neoplasma malignum generalisatum. Acta Derm Venereol (Stockh) 120(suppl):96, 1985.

38. Delattre JY et al: Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. Neurology 38:194, 1988 .

39. Trump DL et al: Epidermolysis bullosa acquisita. JAMA 243:1461, 1980.

40. Green ST, Natarajan S: Linear IgA disease and oesophageal carcinoma. J R Soc Med 80:48, 1987.

41. McEvoy MT, Connolly SM: Linear IgA dermatosis: Association with malignancy. J Am Acad Dermatol 22:59, 1990.

42. Wilson JF et al: Herpes zoster in Hodgkin's disease. Cancer 29:461, 1972.

43. Rusthoven JJ et al: Varicella-zoster infection in adult cancer patients. A population study. Arch Intern Med 148:1561, 1988 .

44. Shneidman DW et al: Chronic cutaneous herpes simplex. JAMA 241:592, 1979.

45. Rigel DS, Jacobs MI: Malignant acanthosis nigricans: A review. J Dermatol Surg Oncol 6:923, 1980.

46. Ollendorff-Curth H: Significance of acanthosis nigricans. Arch Dermatol 66:80, 1952.

47. Wilgenbus K et al: Further evidence that acanthosis nigricans maligna is linked to enhanced secretion by tumor of transforming growth factor alpha. Arch Dermatol Res 284:266, 1992 .

48. Howel-Evans W et al: Carcinoma of the oesophagus with keratosis palmaris et plantaris (tylosis). Q J Med 27:413, 1958.

49. Harper PS et al: Carcinoma of the oesophagus with tylosis. Q J Med 30:317, 1970.

50. Blanchet-Bardon C et al: Hereditary epidermolytic palmoplantar keratoderma associated with breast and ovarian cancer in a large kindred. Br J Dermatol 117:363, 1987.

51. Dobson RL et al: Palmar keratoses and cancer. Arch Dermatol 92:553, 1965.

52. Mortimer P et al: Palmar keratoses and internal malignancy. Br J Dermatol 109:21, 1983.

53. Andreev VC: Skin manifestations in visceral cancer, in Current Problems in Dermatology, series editor, H Mali. Basel, Karger, 1978.

54. Breathnach SM, Wells GC: Acanthosis palmaris: Tripe palms. A distinctive pattern of palmar keratoderma frequently associated with internal malignancy. Clin Exp Derematol 5:181, 1980.

55. Lo WL, Wong CK: Tripe palms: A significant cutaneous sign of internal malignancy. Dermatology 185:151, 1992.

56. Bazex A, Griffiths A: Acrokeratosis paraneoplastica —a new cutaneous marker of malignancy. Br J Dermatol 102:301, 1980.

57. Baran R: Paraneoplastic acrokeratosis of Bazex. Arch Dermatol 113:1613, 1977.

58. Bolognia JL: Basex syndrome: Acrokeratosis paraneoplastica. Semin Dermatol 14:84, 1995.

59. Tuffanelli DL, Winkelmann RK: Systemic scleroderma. Arch Dermatol 84:359, 1961.

60. Haggani MT, Holti G: Systemic sclerosis with pulmonary fibrosis and oat cell carcinoma. Acta Derm Venereol (Stockh) 53:369, 1973.

61. Muir EG et al: Multiple primary carcinomata of the colon, duodenum and larynx associated with kerato-acanthomata of the face. Br J Surg 54:191, 1967.

62. Torre D: Multiple sebaceous tumours. Arch Dermatol 98:549, 1968.

63. Burgdorf WH et al: Muir-Torre syndrome. Histologic spectrum of sebaceous proliferations. Am J Dermatopathol 8:202, 1986.

64. Housholder MS, Zeligman I: Sebaceous neoplasms associated with visceral carcinomas. Arch Dermatol 116:61, 1980.

65. Schwartz RA et al: The Torre syndrome with gastrointestinal polyposis. Arch Dermatol 116:312, 1980.

66. Gardner EJ: A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. Am J Hum Genet 3:167, 1951.

67. Lynch PJ: Nevoid basal cell carcinoma syndrome with features of Gardner's syndrome. Cutis 16:905, 1975.

68. Gentry WC et al: Multiple hamartoma syndrome (Cowden's disease). Arch Dermatol 109:521, 1974.

69. Brownstein MH et al: Cowden's disease. Cancer 41:2393, 1978.

70. Taylor AJ et al: Alimentary tract lesions in Cowden's disease. Br J Radiol 62:890, 1989.

71. Bader JL: Neurofibromatosis and cancer. Ann N Y Acad Sci 486:57, 1986.

72. Das Gupta TK, Brasfield RD: von Recklinghausen's disease. Cancer 21:174, 1971.

73. Fitz Patrick's Dermatology in General Medicine, fifth edition, Vol.2, p 1783-1796, 1999.

74. Gorlin RJ: Nevoid basal cell carcinoma syndrome. Medicine (Baltimore) 66:98, 1987.

75. Gorlin RJ et al: The multiple basal cell nevi syndrome. Cancer 18:89, 1965.

76. Graham JH, Helwig EB: Bowen's disease and its relationship to systemic cancer. Arch Dermatol 80:133, 1959.

77. Reymann F et al: Relationship between arsenic intake and internal malignant neoplasms. Arch Dermatol 114:378, 1978.

78. Rubinstein N et al: Generalized pruritus as a presenting symptom of phenytoin-induced Hodgkin's disease. Int J Dermatol 24:54, 1985 .

79. Wasserman LR: The treatment of polycythemia vera. Semin Hematol 13:57, 1976.

80. Newbold PCH: Skin markers of malignancy. Arch Dermatol 102:680, 1970.

81. Gammel JA: Erythema gyratum repens. Arch Dermatol Syphilol 66:494, 1952.

82. Appell ML et al: Erythema gyratum repens. Cancer 62:548, 1988.

83. Radin DR et al: Pancreatic acinar cell carcinoma with subcutaneous and intraosseous fat necrosis. Radiology 158:67, 1986.

84. Sweet RD: An acute febrile neutrophilic dermatosis. Br J Dermatol 76:349, 1964.

85. Hickman JG. Pyoderma gangrenosum. Clin Dermatol 1983; 1:102-13.

86. Powell FC, Daniel Su WP, Perry HO. Pyoderma gangrenosum: classification and management. J Am Acad Dermatol 1996; 34: 395-409.

87. Hensley GT, Glynn KP: Hypertrichosis lanuginosa as a sign of internal malignancy. Cancer 24:1051, 1969.

88. McLean DI, Macaulay JC: Hypertrichosis lanuginosa acquisita associated with pancreatic carcinoma. Br J Dermatol 96:313,1977.

89. Jemec GBE: Hypertrichosis lanuginosa acquisita. Arch Dermatol 122:805, 1986.

90. McGavran MH et al: A glucagon-secreting alpha-cell carcinoma of the pancreas. New Engl J Med 274:1408, 1966.

91. Wilkinson DS: Necrolytic migratory erythema with carcinoma of the pancreas. Trans St John's Dermatol Soc 59:244, 1973.

92. Mallinson CN et al: A glucagonoma syndrome. Lancet 2:1, 1974.

93. Minna JD: Neoplasms of the lung, in Harrison's Principles of Internal Medicine, 14th ed, edited by AS Fauci et al. New York, McGraw-Hill, 1998, p 552.

94. Giardiello FM et al: Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 316:1511, 1987.

95. Venencie PY, Perry HO: Sign of Leser-Trélat: Report of two cases and review of the literature. J Am Acad Dermatol 10:83, 1984.

96. Rampen HJ, Schwengle LE: The sign of Leser-Trélat, does it exist? J Am Acad Dermatol 21:50, 1989.

97. Kauppinen R, Mustajoki P: Acute hepatic porphyria and hepatocellular carcinoma. Br J Cancer 57:117, 1988.

98. Lookingbill DP et al: Skin involvement as the presenting sign of internal carcinoma —a retrospective study of 7616 cancer patients. J Am Acad Dermatol 22:19, 1990.

99. Tharakaram S. Metastases to the skin. Int J Dermatol 1988;27:240-2.

100. Brownstein MH & Helwig EB: pattrns of cutaneous metastses. Archives of Dermatology Vol.84, p 862 – 868, June 1972.

101. Anhalt GJ et al: Paraneoplastic pemphigus: the role of tumours and drugs. Br J Dermatol 114:1102. 2001.

102. Shanbrom et al. herpes Zoster in hematologic neoplasias; some unusual manifestations. Ann Intern Med 1960; 53; 523 – 33.

PROFORMA

Cutaneous Manifestations of Internal Malignancy

S.No. :
Name : Age: Sex:
Address : Occupation:
OP/IP No.
C.No.

Primary Neoplasm:
Symptoms / Duration :
System Involved :
Type of Neoplasm :

Date of Diagnosis :

Investigations :

Cutaneous lesions:
Symptoms / Duration :
Morphology :
Number :
Site :
Distribution :
Provisional Diagnosis :
Investigations :
Tzanck/KOH smear/ FNAC/Histopathology:

General condition :

System Examination :

Follow up :